DISSERTATION ON

A STUDY ON ESTIMATION OF SERUM URIC ACID LEVELS IN ESSENTIAL HYPERTENSION

Dissertation Submitted To

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY,

In partial fulfillment of the

rules and regulations, for the award of the

M.D. DEGREE IN GENERAL MEDICINE

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THANJAVUR – 613004

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CERTIFICATE

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I , **DR.ELLANGOVAN.M** , solemnly declare that the dissertation titled "**A STUDY ON ESTIMATION OF SERUM URIC ACID LEVELS IN ESSENTIAL HYPERTENSION"** is a bonafide work done by me at Thanjavur Medical College , Thanjavur during **2016 January to 2016 June** under the guidance and supervision of **Prof.Dr.C.Paranthakan.M.D** Unit Chief Department Of Internal Medicine, Thanjavur Medical College, Thanjavur. This dissertation is submitted to Dr . M.G.R Medical University , Tamilnadu towards the partial fulfilment of requirement for the award of **M.D. Degree (Branch -1) in General Medicine**

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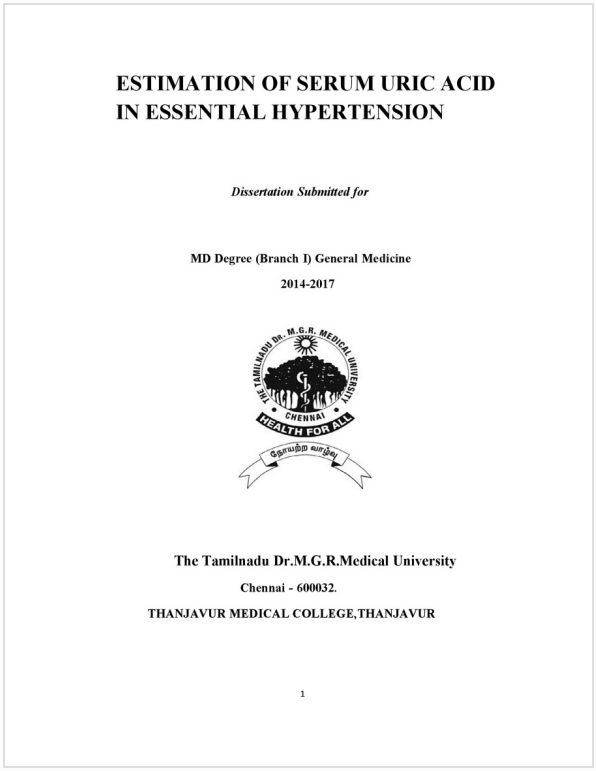

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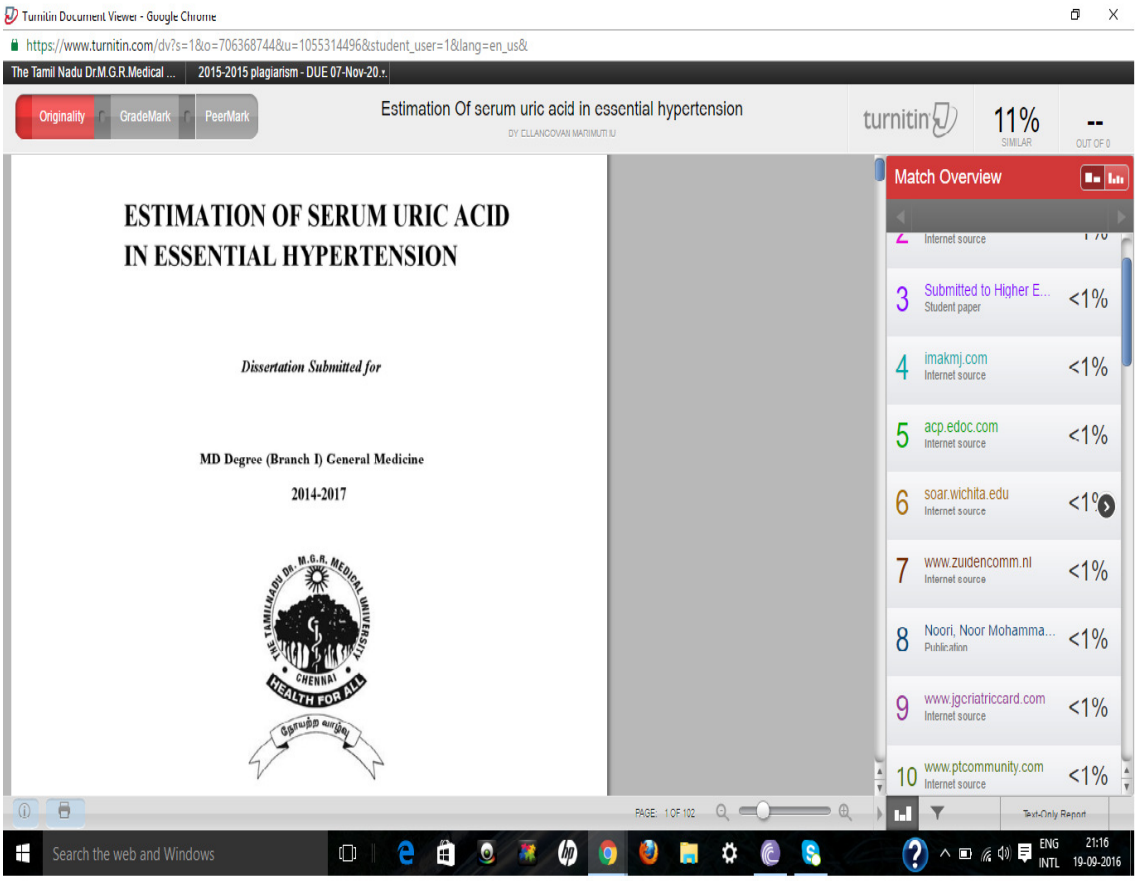
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CONTENTS

INTRODUCTION

Cardiovascular disease is an important epidemic of the public health. Approximately more than seven million deaths worldwide were attributable to high blood pressure in the year 2000. SHT is one of important vascular diseases, prevalence is about twenty five percent of individuals and increases with older age individuals. The cardiovascular risk factors associated with blood pressure depend upon combination of risk factors such as age, gender, weight, physical activity, smoking , family history , serum cholesterol, pre existing vascular disease.

The various investigations have proved that SUA has been associated with cardiovascular morbidity and cardiovascular diseases. CANON et al (1968) found that elevated SUA was found in twenty six percent of untreated hypertensive patients, fifty percent of treated patients.

Yeong do shu et al (1986) has observed the relationship of essential hypertension and hyperuricemia. He reported that the mean concentration of serum uric acid in essential hypertensive is significantly higher in comparison with normotensive individuals. Yeong do shu et al (1986) reported elevated SUA is found to be associated as risk factor for organ damage in SHT.

Fessel et al (1973) studied the co relation between the BP level and SUA levels. He found that increased SBP level in elevated SUA levels. Meyers (1968) published the association between elevated SUA in relation to the SHT.

There are many studies regarding elevated SUA levels and elevated lipid levels in hypertensive patients and target organ damage like MI patients, PVDs etc.

Adlersberg et al (1949) observed the elevated serum uric acid levels in 1/3rd of patients with dyslipidemia in hypertensive group, and later, Harresh-Jones et al confirmed this finding and Becker et al found that fifty percent of patients diagnosed with gout had elevated lipid levels. Feldman detected the elevation of SUA is associated with elevated serum TGL and not associated elevated cholesterol level. This is confirmed by studies conducted by Meyers et al.

Mansara kuwabara et al (2004) has studied the relationship between the serum uric acid levels in essential hypertensive patients in Japanese individuals. Hyperuricemia is associated with lifestyle-related diseases. Approximately twenty five to forty percent of untreated hypertensive patients have concomitant elevated serum uric acid levels. In various studies there were relationship between the elevated SUA and SHT.

PIUMA study (2000) found that uricosuric drugs have decreased the BP in adult patients, suggesting that SUA is the risk factor for the advancement of systemic hypertension. Other reports, including the SHEP study, LIFE study and Framingham study, have observed an co relation between elevated serum uric acid levels and cardio vascular diseases in essential hypertensive patients.

Mazzali et al (2000) has demonstrated that rats found to have increased serum uric acid levels which develop hypertension and associated with preglomerular vascular disease.

Bogalusa study found that of development of diastolic hypertension in childhood patients who developed 10 years later, can be predicted from the serum uric acid levels. Then Framingham group, detected the association between SUA and SHT. In many recently diagnosed systemic hypertensive patients there were increased SUA levels. In 88% of recently detected systemic hypertensive patients there were SUA levels more than six mg per deciliter. There is no elevation in non hypertensive patients.

The body mass index and renal function was not directly related to the SUA. Finally, pilot major studies observed that uricosuric drugs in the essential hypertensive individuals who had decrease blood pressure receiving the uricosuric drugs and also it was found placebo was not carried out.

The SUA is a strong marker of risk for the advancement of SHT. This co relation is not dependant of alcohol consumption, lipid levels , organ failure.

The co-relation of elevated uric acid levels in essential hypertension has been observed for very long time. It is unclear about the association between elevated SUA and SHT because of baseline elevated lipd levels and kidney damage. The under perfused kidneys have been associated with elevated uric acid levels because of reduced excretion of UA from kidney tubules.

Elevated insulin levels in blood may also associated with elevated uric acid levels with SHT. Several studies found that uric acid may in fact have a role in development of essential hypertension. Elevated uric acid causes elevated blood pressure in experimental animals, that corrects with urosuric drugs.

This co relation was not depentant of age, weight, BMI, total cholestrol, TGL , cigarette, consumption of alcohol and blood sugar. They found that elevated SUA is a strong indication of advancement of SHT.

Here an attempt has been made to revise the estimation of elevated uric acid levels in essential hypertension and the correlation and association between elevated uric acid levels and hypertensive target organ damage.

AIMS AND OBJECTIVES

1. To study the level of uric acid in patients with essential hypertension

2. To identify whether any association exists between ages, sex, body mass index, smoking, and target organ damage and the presence of elevated serum uric acid

REVIEW OF LITERATURE

HYPERTENSION

Hypertension is one of the common life style disorder and is a very strong risk factor for cardiovascular disorder. It is estimated that it increases the risk atleast two fold for cardiovascular disorders including coronary diseases , Heart failure conditions /stroke conditions , kidney failure and small vessel diseases. Usually the others like diabetes and dyslipidemia are also commonly associated with hypertension.

Hypertension is a global disease but its prevalence varies among countries and sub populations. The hypertension incidence in individuals increases with advanced age and it is estimated that starting from around 15% to 20% in early age, it increases to 75% to 80% in individuals above 70 years of age. The framingham Study have observed that hypertensive patients have a four fold rise in cererbrovascular accidents, six fold rise in congestive Heart failure, When compared to Normotensive control subjects. It has been estimated that several small regional surveys in urban population have reported a prevalence of 6.1% to 36.3% in men and 2% to 39.4% in women and from 2 % to 36 % in men and 5.8% to 37.2 % in women in rural area hypertension.

Epidemiological studies suggest that 20% to 60% of essential hypertension is inherited and reaminder is acquired or environmental. Increased weight found to be major factor for the development of hypertension. The Framinghaam study showed approximately 1 mmhg rise of Systolic blood pressure for every 1.25 kg of weight gain. Abdominal obesity as evidenced by waist circumference of 80 cm in women and 90 cm in men has also been found to be associated with risk for hypertension.

Individuals have low blood pressure in those who consume salt less than three gram per day. The Intersalt study in (n 10,079) men and women from 32 countries, it was observed that 100mg ,lower salt intake resulted was in lower increase in BP by 9 mmhg in the age group 25 years to 55 years. The Intersalt study demonstrated a association between the consumption of salt and BP among communities.

MECHANISMS OF HYPERTENSION

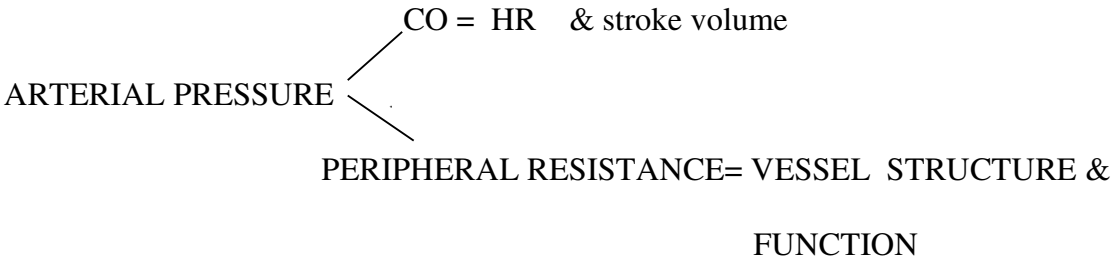
The factors should be sought out to understand the regulation of both normal BP and increased BP. The stroke volume and heart rate are the two main factors in calculating the cardiac output. Arterial pressure mainly depend upon the CO and resistance in the peripheral vessels. The contraction and compliance of the myocardium is the main factors of stroke volume. The resistance in peripheral vessels mainly depend on the changes in small peripheral verssels.

INTRAVASCULAR VOLUME

The extra cellular volume is mainly depend on Na+ ion in the ECF. The fluid in the vascular compartment increases if the NACL consumption increases with capacity of the level of kidney to eliminate the NACL and finally CO will increase. There is normally the autoregulation of blood vessels in order to maintain to normal blood flow even if there is elevated blood pressure so the resistance in vessels must increase.

$$BP = \frac{\text{pressure in the blood vessels}}{\text{Resistance in the vessels}}$$

The first response to rise in blood pressure is the increased CO due to increased fluid in ECF. Later, the resistance in peripheral vessels predominante and cardiac output will be normal. The sodium chloride, can activate several mechanisms all of which can increase the blood pressure. The sodium with chloride has the main effect of the elevated blood pressure. As sodium chloride consumption increases, its elimination in the urine rises and finally blood pressure increases in order to maintain the Na balance. The possible mechanisms that involve in natriuresis are increase in GFR, increase elimination through kidney tubules and secretion of ANP. In conditions where there is elimination of NACL is not adequate, the blood pressure increases to maintain the natriuresis and Na+ balance.



AUTONOMIC NERVOUS SYSTEM

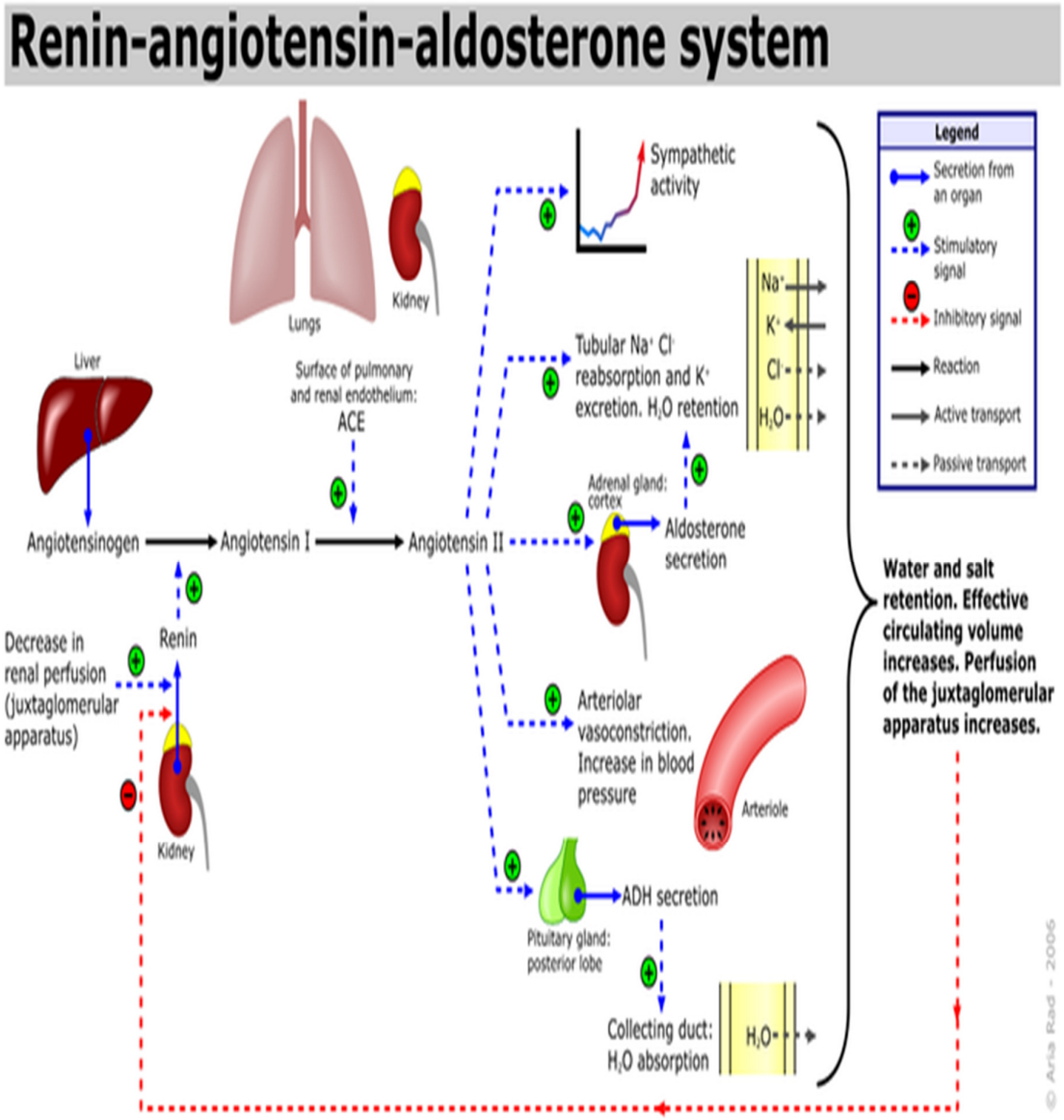
The baro receptors increases in response to the elevated blood pressure due to decrease in sympathetic out flow and leads to decrease in BP and HR. The blood pressure levels are maintained during postural changes, stress situations is mainly through this mechanisms. Baro-receptor adapt itself to the sustained increased BP and are reset to the elevated BP. Patients with autonomic neuropathy and impaired baro-receptor function leads to elevated BP levels and tachycardia.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

This mechanism regulates the blood pressure via angiotensin II and aldosterone, which causes vasoconstriction and retention of sodium respectively. The 3 main mechanism of RAAS activation is 1) the transport of Na in the loop of henle that activate the macula densa of the afferent arteriole. (2) reduced pressure in the afferent arteriole and (3) activation of sympathetic nervous system. The result is high secretion of aldosterone.

The aldosterone act on many tissues and alter the morphology and functions of the vital organs like heart , renal and vascular changes which lead to structural changes like myocardial fibrosis and cortico medullary sclerosis in the kidneys and blood vessel inflammation. These effects are increased by increase Na consumption. Spironolactone prevents fibrosis in ventricle by inhibiting aldosterone effects.

The elevated blood pressure is not directly related to the increase RAAS system activation. Because the RAAS system get activated if there is low Na or decreased BP. The RAAS activity also observed in heart failure and hepatic failure in absence of hypertension which s referred as secondary aldosteronism.



In hypertensive heart disease patients the LVH is related to the high levels of serum aldosterone levels.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

1. HEART

The long standing hypertension leads to structural and functional changes of the heart leads to LVH , heart failure with derpressed ejection fraction , congestive cardiac failure , alterations in the of blood flow in the blood vessels due to atherosclerotic changes and finally leads to CAD and peripheral vascular disease and heart conduction abnormalities and tachy and brady arrthymias.

Heart failure with depressed ejection fraction is one of the target organ damage due to hypertension related cardiac manifestations and is aggravated by LVH and coronary artery disease.

2. BRAIN

Another one of important target organ damage for hypertension is cerebrovascular disease , which comprises of hemorrhages and infarction in the brain. The person above age of sixty five years old, particularly with increased systolic pressure , the prevalence of cerebrovascular accident rises with increases morbidity and mortality.

One of manifestation of long standing HTN results in memory disturbances in older individuals. Hypertensive encephalopathy is due to the impaired autoregulation in the blood vessels in cerebral blood vessels at increased threshold level, resulting in dilation of blood vessels due to

increased vascular permeability and increased perfusion. It one of condition which leads to rapid progression to detoriation of mental status and increased morbidity and mortality.

3. KIDNEY

Another important target organ damage is kidney failure and end stage renal disease. The increased damage is associated with long standing hypertension with increased blood pressure above the threshold which is graded and present persistently. It has been related to increased systolic BP compared to diastolic BP.

The main pathological changes in the renal damage is changes in structure and functional alteraltion in afferent glomerular arterioles results in alteration in blood flow patterns in the nephron structures including glomeruli and other structures including tubular changes. The main pathological changes is fibrosis and afferent arteriosclerosis and including damage to the renal tubules.

The result is abnormal urine albumin secretion which is result of glomerular damage and it is early indicator of renal failure which can be detected through normal urine dip stick test which detects micro- albuminuria less than 300 microgram and macro-albuminuria and also can be found out by urine protein-creatinine ratio.

4. PERIPHERAL ARTERIES

One of the important target organ damage is disease of peripheral blood vessel which is important indicator of on going coronary artery disease and CVDs. The important screening tool in detecting the atherosclerotic changes of peripheral blood vessels is by Doppler ultrasound study which is useful in detection of ABP index. It is ratio of blood pressure in the ankle to blood pressure in the arm. Mainly systolic blood pressure is calculated , the principle is compared to upper limb, the lower BP in the ankle is indicative of atherosclerotic changes in the lower limbs. An **ABPI** less than 0.90 is considered as arterial disease and less than 0.50 as severe arterial disease.

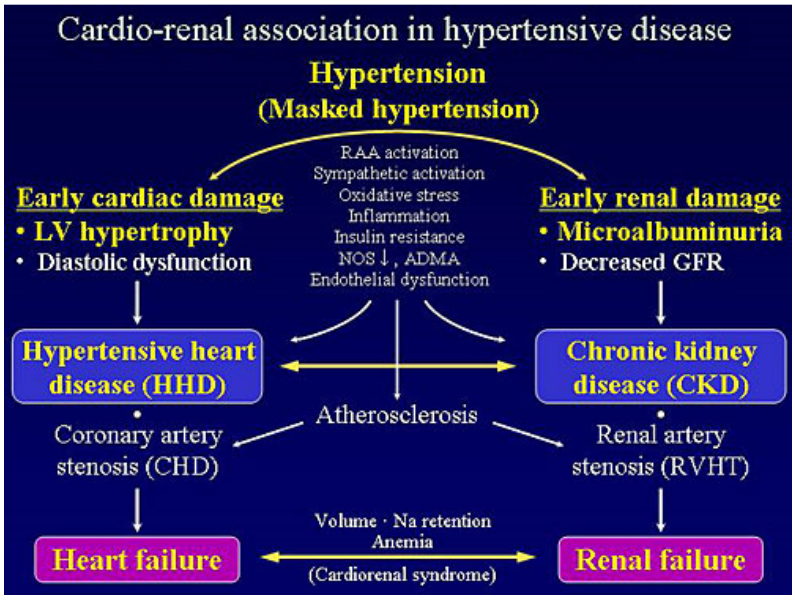


Figure 1 TARGET ORGAN DAMAGE

DEFINING HYPERTENSION

As per epidemiology there is no blood pressure level that defines HTN. The trial study which included more than 300,000 individuals that presented with persistent blood pressure and rating the consequences of both SBP and DBP on target organ damage and mortality.

For every twenty mmhg rise in SBP and ten millimeter of mercury rise in DBP the risk of CVDs doubles. Among aged persons, systolic BP and pulse pressure are the important risk assessment of CVDs than diastolic blood pressure.

CRITERIA

In the general population of individuals aged more than 60 years, anti-hypertensives should be started if SBP is 150 mm Hg or more , or if DBP is 90 mm Hg or more. The drug therapy does not need modification if BP is less than 140 mm Hg, unless if associated with side effects on individual health condition.

The individuals aged less than 60 years and below, drug therapy is to be started if SBP is 140 mm Hg or more, and if DBP is 90 mm Hg or more. The target SBP is should be below 140 mm Hg, and the target diastolic BP should be below 90 mm Hg.

Classification of Blood Pressure for Adults

Classification based on the eighth report of JOINT NATIONAL COMMITTEE on detection , assessment and management of hypertension (JNC 8).

JNC VIII Classification

Blood Pressure Classification	**Systolic, mmHg**	**Diastolic, mmHg**
Normal	<120	and <80
PRE HTN	120-139	or 80-89
STAGE I HTN	140-159	or 90-99
STAGE II HTN	≥ 160	or ≥ 100
Isolated systolic HTN	≥ 140	And ≤ 90

ACCURATE BLOOD PRESSURE MEASUREMENT

The blood pressure must be measured correctly for therapy. The equipment whether aneroid, mercury or electronic, should have a consistent technique which is frequently standardized and and the patient must be in properly positioned. Initially auscultatory method should be done.

Individuals quietly seated for five minutes in a chair and arm supported at heart level. Coffee , exercises and tobacco products are avoided thirty minutes before measurement. The BP also measured in standing position who complaints of symptoms suggestive of orthostatic hypotension. The cuff

size should be 80% of the arm size. Two measurement of BP will have to be checked.

In order to measure the SBP the radial pulse closure pressure and the inflation should be twenty to thirty millimeter of mercury. The cuff deflation rate should be two mm Hg per second for auscultatory findings. The first korotkoff sound that is phase I is the SBP and last disappearance of korotkoff sound phase 5 is the DBP.

In some of conditions like incompetence of aortic valve, the diastolic blood pressure will be zero mm Hg and first muffled sound is found as diastolic blood pressure. Be concerned while detecting BP in older individuals as there will be auscultatory gap.

Recommendations for Follow-Up Based on Initial Blood Pressure Measurements for Adults without Acute End Organ Damage (JNC-8).

Initial Blood Pressure, mm Hg*	**Follow –Up Recommended+**
Normal	Recheck in 2 years
PRE HT	Recheck in 1 Year
Stage 1 HT	Confirm within 7 days to2 Months
Stage 2 HT	Need further evaluation or refer to source of care within 1 month. Increased pressures (eg.>170/120mm Hg) evaluate and manage immediately or alteast in 1 week depending on clinical scenario.

The important strategy in therapy is life style modification (LSM) which is given in JNC VIII. The DASH method of treating the patients is modification in eating habits, decreased salt consumption, decreased foods with high saturated fatty acid. The aerobic activity should be carried out. The alcohol consumption should be less than two drinks daily in men and one drink daily in women. One drink constitutes twelve ounces of beer, five ounces of wine, or one and half ounces of liquor. Stopping the smoking also reduces cardiovascular risk.

In individuals with age more than 50, SBP more than 140 mm Hg is one of the risk factor of CVD than DBP. Beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg.

Those who are normotensive at 55 years of age will have a 90% life time risk of developing hypertension.Prehypertensive individuals require health promoting lifestyle modifications to prevent the progressive rise in blood pressure and Cardio-vascular disease.

For uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most patients, either alone or combined with drugs from other classes.

Two or more antihypertensive drugs will be required to achieve goal BP (<140/90 mm Hg or <130 mm Hg) for patients with diabetes and chronic kidney disease.

For patients whose BP is more than 20 mm Hg above the systolic BP or more than 10 mm above the diastolic BP , initiation of therapy should be using two agents, one of which usually will be a thiazide diuretic, should be considered.

CLINICAL DISORDERS OF HYPERTENSION

1. ESSENTIAL HYPERTENSION
2. METABOLIC SYNDROME
3. RENOVASULAR HYPERTENSION
4 PRIMARY ALDOSTERONISM
5. CUSHING'S SYNDROME
6. PHEOCHROMOCYTOMA
7. MISCELLANEOUS CAUSES OF HYPERTENSION

Obstructive sleep apnea, Coarctation of the aorta, acromegaly, hypercalcemia, both hypo and hyper thyroidism.

8. MONOGENIC HYPERTENSION

ESSENTIAL HYPERTENSION

Essential hypertension is associated with familial predisposition and not as relationship between the genetic and environment factors. The advancing age has higher incidence of essential hypertension. In many individuals with SHT the resistance in blood vessels increases and CO remains normal. In individuals with age less than thirty the resistance in the blood vessels remains normal and CO is increased. The vasoconstriction is seen in hypertensive individuals with high renin and those with low renin have volume dependant hypertension.

Overall Cardiovascular Risk:

The CVD risk can be predicted by following factors:

1. The stage of HT.
2. The association of target organ damage.
3. The associated CVD risk factors. (Jackson, et a11993)

The Aim of anti-hypertensive therapy should not only decrease the blood pressure but also include risk factors. The major CVDs indicated in JNC-VIII report are:

- Hypertension
- Tobacco smoking
- Obesity

- physical inactivity
- Abnormal lipid levels
- DM
- Micro - albuminuria or estimated GFR 60 < ml/min
- Age (> 55 for men , >65 for women)
- Family history of premature CVD (less than 55 for men, Less than 65 for women)

URIC ACID METABOLISM

The uric acid is produced via exogenous and also endogenous sources. The SUA levels in the body is manily determined by production and excretion by the kidneys and gut. The various enzymes are involved in production of purine and its degradation. Urates, in ionized form of uric acid, most abundant in ECF and synovial fluid, with 96% exist as mono - sodium urate at pH 7.4. The solubility of uric acid in urine is determined by its PH. Purine is mainly present in tissues that is rich in xanthine oxidase enzymes mainly liver and gut tissues. Urate production doesn't depend on the individuals dietary content of purine and the salvage of purine synthesis and its metabolism. The main excretion of urate is by the kidney and remaining is through the intestine.

METABOLISM

The kidneys excrete urate from the body and regulates balance by using definite organic anion transporters (OATs) along with urate transporter I (URATI), then human uric acid transporter (hUAT). Urate transporter I and other organ anion transporter carry urate from the apical epithelium to the tubular cell of kidney. Once they enter into the cell , urate must enter with help of controlled voltage-dependant carrier hUAT to basolateral lumen. Until recently, handling of urate by kidneys have been described using component model. These are the following methods :

(l) GFR (2) Reabsorption in tubules,

(3) Tubular Secretion, and

(4) Post secretory reabsorption

Urate transporter I is expressed in the proximal nephron's apical brush border. Uric acid metabolites exhibit mechanism known as cis – inhibition by which it inhibit urate transporter I on the tubular cell.

The total-body urate availability in the body is the net balance between urate synthesis and excretion

The synthesis of urate is greatly depend on the purines intake in the individual's diet and the rates of endogenous biosynthesis of purines from non-purine precursors, Nucleic acid of tissues and salvaging phosphori-bosyl-

transferase activities. The urate excretion from the body has already been described above. Hyperuricemia is due to the imbalance between the production and excretion. Tophi is due to deposition of urate crystals in the tissues.

Purines are produced by the human from amphibole intermediate products. Purines are not routinely found in the diet. The sources of mechanism of purine synthesis by 3 sources:

- Denovo synthesis
- Dietary nucleic acids
- Cellular nucleic acid

Denovo production of urate:

The aminoacids like aspartate and glutamate compound are the sources of purine atom ring , CO2 and derivates of tetrahydrofolate. Then the purine ring is produced from eleven step process in which inosine-monphosphaste is produced. Then inosine-monophosphate is converted to either adenosine monophosphate (AMP) or Guanine mono phosphate (GMP). The first step is production of phosphoribosyl pyrophosphate (PRPP). Then Using PRPP as substrate, phosphoribosyl amine and glutamine is synthesized and is catalysed by the enzyme amino-phosphoribosyl transferase. This is the rate limiting step in purine synthesis.

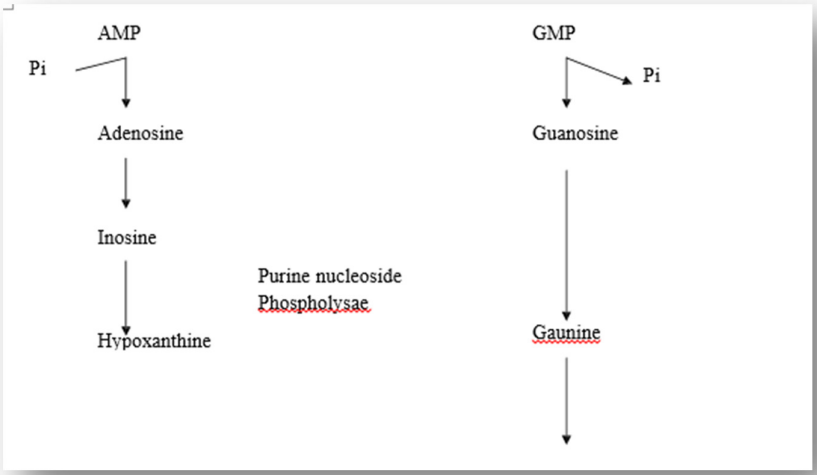
Salvage Pathway for Purines

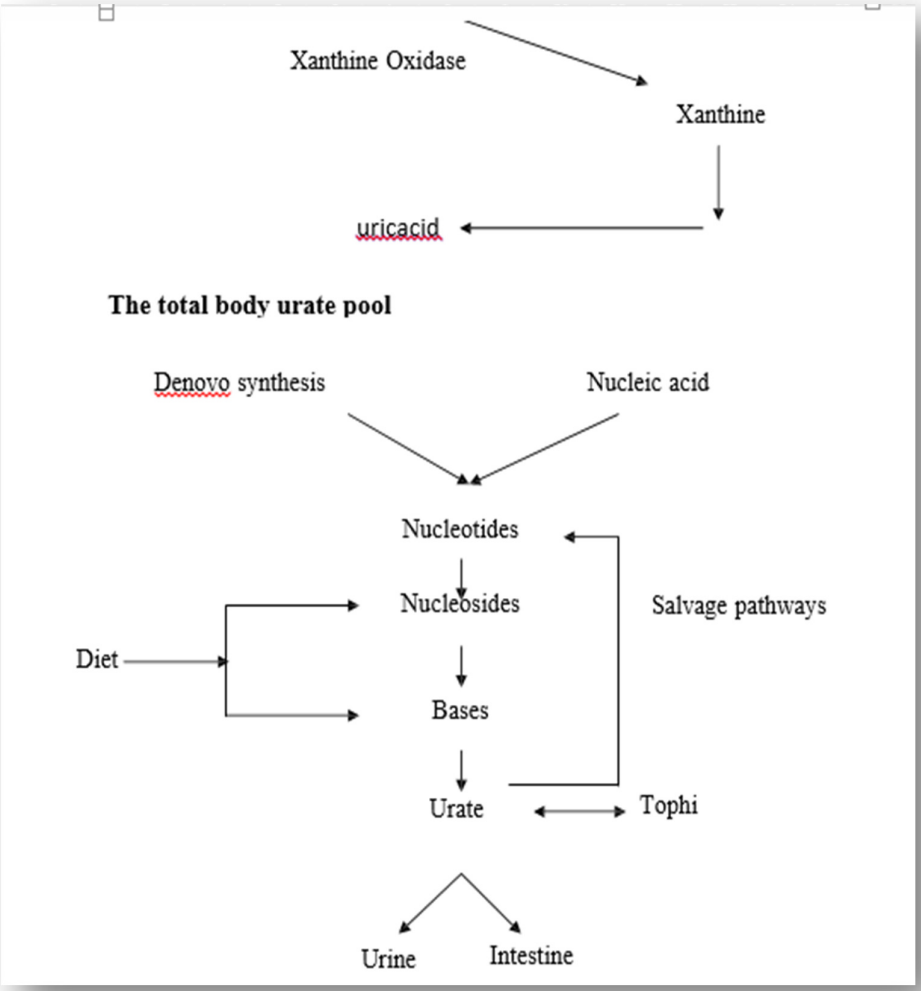
All the purines need not be metabolized to uric acid. Purines which is end product of cellular nucleic acid can be recycled to nucleotides and utilized by the body. There are two enzymes that include adenine-phosphoribosyl-transferase (APRT) and Hypoxanthine guanine-phosphoribosyl-transferase (HGPRT). Deficiency of HGPRT causes Lesch-Nyhan syndrome.

Uric Acid Metabolism

The total urate pool which is expressed as uric acid in the body is about 1200 mg in which through denovo synthesis 300-600 mg is producued and purines synthesis from the diet is about 600-700 mg. Everyday two third of uric acid are excreted via urine and one third is eliminated through process in the gut known as uricolysis.

Degradation of Purines - Production of Uric Acid





The Urate is handled by kidneys through following :

i. GFR is 100% of the filtered load.

ii. 99% of filtered load is absorbed through proximal tubule.

iii. 50% of filtered load is secreted through tubular cells

iv. 40% of secreted filtered load is again reabsorbed.

10 percent of filtered load is the net clearance and the net filtration rate is 6 to 11 ml min/ 1.73 m2.

Plasma Urate Levels:

As mentioned previously, the ionized form of uric acid that is monosodium urate is present in plasma and synovial fluid.

Normal serum uric acid level in males ranges from 3.1to 7mg/dl and in females from 2.5 to 5.6mg/dl.

Monosodium urate get saturated with plasma at levels of 415 micromol/L (6.8 mg/dl) at 37°C. If the concentration is more than the normal, then urate is supersaturated with plasma and it creates a potential for crystal precipitation. But due to the neutralizing substances in the plasma precipitation does not occur even at higher concentrations in the plasma.

Plasma urate levels elevates at puberty with female uric acid levels being lower than in men, until menopause after which it gradually rises to male value. It decrements during gravidity. Hyperuricemia is a one of the early feature of pre-eclampsia.

Extrinsic factors, concretely diet, plumbism, with high alcohol consumption in the society and diseases like malaria, thalassemia can affect SUA levels distribution in different populations. Epidemiological studies show paramount variations in serum uric acid levels between different ethnic groups. For eg, Polynesians have higher level of uric acid than western Europeans and white Americans. This explains the genetic, especially, polygenic influence in the control of serum uric acid. Other survey studies accentuate the paramountcy of environmental factors of purine, protein and alcohol intake. For example Gress and Zollner (1990) showed that the

cumulated frequency of plasma urate rose from 6.2 mg/dL to about 9.0 mg/dl between 1962-1971 in sodality with amended nutritional state of Bovarian population

The frequency distribution of serum urate levels predicated on asymptomatic population is only approximately gaussian, with an excess of higher values due to inclusion of some asymptomatic hyperuricaemic subjects. In view of asymmetrical distribution of frequency and normality definition, as the mean value plus two SD above the mean , normal upper limit of 7.0 mg/dL (420 f.1moVL) for men and 6.0 mg/dL (360 f.1moVL) for women is widely adopted.

Hyperuricemia

Elevated SUA levels is mainly due to the imbalance between the production and elimination. When sustained elevated SUA subsists, the plasma are super saturated with urate and total body urate is rised.

The concentration of urate that exceeds limits in the plasma 415mol/l (6.8mg/dl) is referred as hyperuricemia. In several studies, hyperuricemia is defined as the mean plus 2 SD of values randomly choosed from population.determined from a healthy population.

CAUSES OF HYPERURICEMIA

Hyperuricemia is divided into primary disorder and secondary disorder.

However, it is useful to divide the hyperuricemia into primary and secondary that is whether it is due to overproduction or under excretion or the combination of the both.

HISTORY OF URIC ACID AND HYPERTENSION

The possibility that uric acid may be incorporated into SHT. Honestly, in the paper published in 1879 that at first portrayed SHT, Frederick Akbar Mohamed found every of his hypertensive subjects are from families diagnosed with gout. Then he proposed that the advancement of uric acid is mainly is dependant on SUA level.

Following ten years, this hypothesis re-rose when Haig proposed low-purine diets as an approach to check hypertension and blood vessel changes. In1909, the French academician Henri Huchard saw that sclerosis in nephrons was found in (1) individuals with elevated SUA, individuals working in lead factories, and the people who have an eating routine improved with oily meat. These social occasions are associated with elevated SUA.

The relationship between elevated SUA and hypertension was reported on and on in the 1950s to 1980 , however got by and large negligible upheld thought in perspective of nonappearance of a particular clarification.

A majority of adults diagnosed with SHT have elevated SUA levels, (more than 6.5 mg/dl), and In preeclampsia the SUA and hypertension is more than seventy percent

Regardless of perceptions, the absence of specicifcity prompted gentle rises of blood uric acid being to a great extent disregarded in normal practise. The quality of the relationship between SUA and SHT is most important in individuals with young onset hypertension than older individuals.

Cross – sectional studies has confirmed that increased SUA levels is found in untreated patients.

URIC ACID AND CARDIOVASCULAR DISEASE

Over late years there has been discussion about the way of the relationship between raised SUA and heart diseases. The major heart disease such as MI have been associated with SHT , which is reported by several studies. It lead to studies invovling SUA levels in relation with CVDs. The exact role of SUA with heart disease is difficult to substantiate, because of its relation with other cardiovascular morbidities, SHT, DM , elevated total cholestrol levels and obesity.

Nearly 120 years have elapsed since uric acid was first described as a potential factor in the development of cardiovascular disease (Gerteler, et al 1951). Much, but not all epidemiological research identifies hyperuricemia as an independent risk factor for the development of cardiovascular disease and renal disease, particularly in patients with hypertension or congestive

heart failure and in women (Aldermen, 2002, Cohen, et al 1999, Freedman et al 1995).

Several comparative studies have shown the association between the SUA and CADs when compared with the controls.SUA is also rised in the in the siblings of the heart disease patients.

Elevated SUA levels are associated with hypertriglyceridemia, elevated blood sugar levels and other confounding factor, BMI. In most of the hypertensive individuals had elevated SUA and it also predicts the later development of systemic hypertension. There are group of clusters with rising heart diseases associated with elevated SUA levels.They are reported by (Hayden, et al 2004) in

- African American patient group
- Patient groups with excessive alcohol
- Hypertensive patient groups
- Non diabetic individuals with atherosclerotic diseases
- Individuals with heart failure and ischemic CMPs.
- Metabolic syndrome patient groups (with hyper insulinemia, IGT , obesity, dyslipidemia, and hypertension).
- Renal disease patient groups and
- Patients groups taking diuretics.

The mechanisms by which the SUA is elevated in these individual group can be explained. The increased oxidative stress and production of reactive oxygen species is the main mechanism in metabolic syndrome.

Uric Acid in Hypertension:

Hypertension is mostly associated with elevated SUA. It was published by cannon that elevated SUA is reported in hypertensive individuals such as highest in malignant hypertension and also in untreated hypertensive patients.

The following are the several mechanisms involving elevated SUA levels and SHT are:

1. The stimulation of urate absorption in response to the decreased GFR (Mersserli, et al, 1980).
2. Local ischemia in tissues due to the small vessel disease (Ruilope, 1999)
3. Lactate production is rised in response to the tissue ischemia and it leads to decreased urate secretion in the proximal tubule and increased uric acid synthesis due to increased RNA – DNA breakdown and increased purine metabolism.
4. xanthine oxidase is also rised in respone to the ischemia in response to the tissues.

Other factors which may contribute are alcohol abuse (Ramsay, 1979), lead intoxication, obesity and insulin resistance (Galvan et al,1995) and diuretic use.

At atlast several investigations confirmed that urate has direct toxic effect on the tissues due to activation of RASS system after entering the vascular smooth muscle cell and finally, the inflammatory cytokine are secreted like CRP and MCP -1.

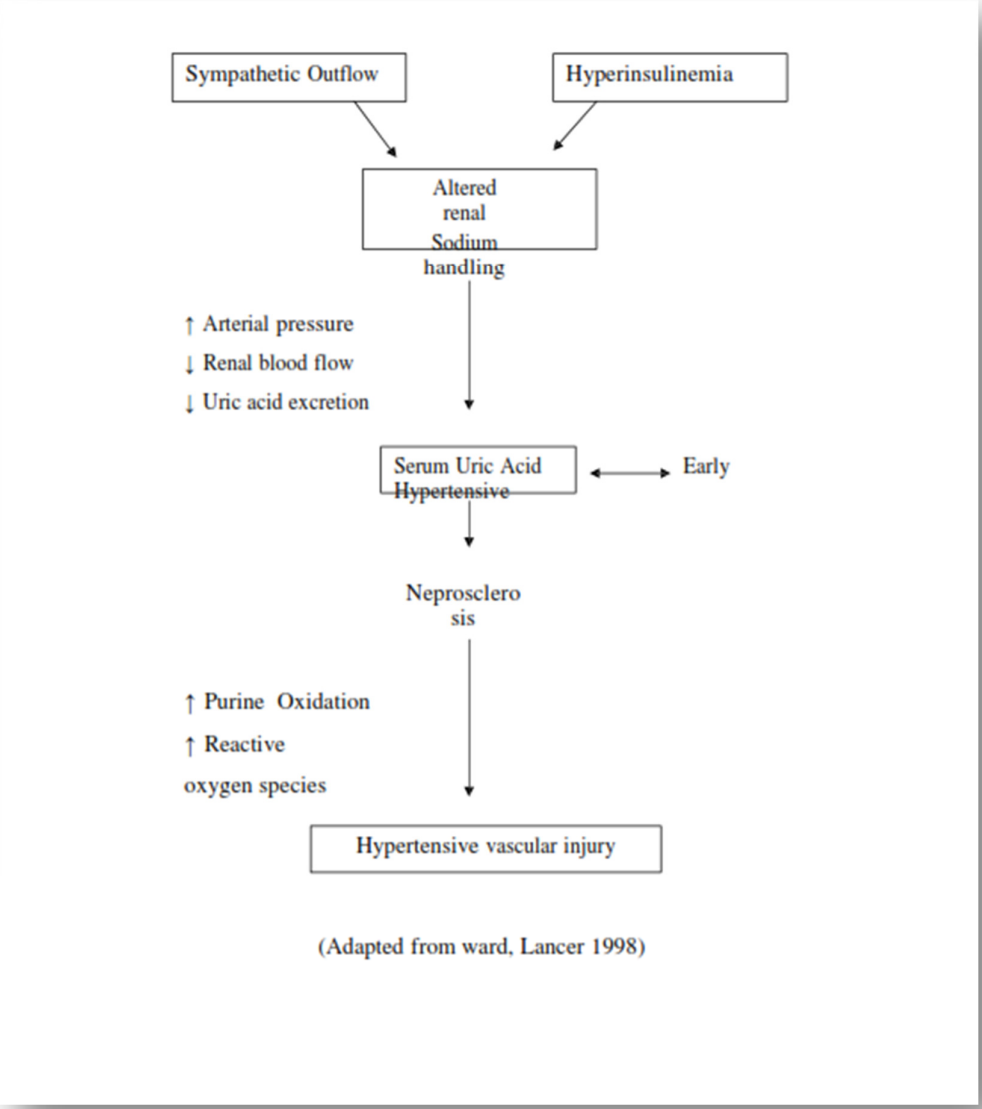
The uric acid causes vasoconstriction via decreased NO synthesis and through activation of RASS system and this hypertensive is mainly salt resistant. Then sustained elevated SUA will result in sustained blood vessel changes and narrowing of the blood vessel occurs progressively and component of hypertension becomes salt dependant and does not depend on uric acid levels.

The elevated uric acid levels in rats causes the activation of RAAS system and decreased NO synthase levels (Marilda Mazzali et al; *Hypertension.* 2001;38:1101.)

It is also possible that metabolic perturbations like Hyperinsulinemia or sympathetic activity may produce alterations in renal sodium handling, leading to increased arterial pressure, decreased renal blood flow and decreased uric acid secretion. This in turn, increases purine oxidation, which results in increased reactive oxygen species, subsequent vascular injury and reduced nitric oxide.

Hyperuricemia and Renal Injury

Pathological changes in the kidneys include afferent arteriole sclerosis and kidney tubular fibrosis , sclerosis in the glomerulus and leads to proteinuria. These pathological alterations can be prevented if SUA is within normal levels. Kidney failure can be estimated from elevated SUA in compared with individuals with normal function.(Johnson, et al, 2003).



(Adapted from ward, Lancer 1998)

Uric acid as a marker of insulin resistance

Syndromes involving insulin resistance has highest incidence in heart diseases due to increase activation of sympathetic nervous system. One of the main feature in insulin resistance syndromes is elevated SUA levels and elevated insulin levels are also associated with hypertriglyceridemia, increased blood sugar levels and increased BMI and waist-hip ratio.

In case of insulin resistance which has blunting action on the glucose metabolism but increased sensitivity on kidney tubules and cause decreased Na+ and urate excretion. Due to elevated insulin levels, that leads to the increased insulin activity on the kidneys, So finally the development of DM and SHT can be estimated from SUA levels even if the individuals have normal creatinine clearance and normal blood sugar levels and finally it can be early marker of insulin resistance syndrome.

So there is non casual relation ship between the SUA and heart diseases with insulin resistance , where CVDs risk is also related to other factors.

Elevated SUA levels are related to the BMI as per studies conducted by the BEDIR et al, and he also found that regulation of SUA by leptin.

Uric acid in relation to injury of the microvessels leading to injury of capillaries and endothelium:

The main mechanism in the elevated SUA levels is mainly due to the elevation of uric acid in males more than 7mg per deciliter and more than 6 mg per deciliter in females and is one of the factor involved in microvessel injury and finally leading to endothelial changes and activation of oxidative damage to vessel wall. (Hayden, 2002; Fang, Alderman 2000).

Uric Acid as Antioxidant:

Uric acid is can also function as anti oxidant. Urate can deactivate the super oxide, OH radical and can chelate iron radicals. The super oxide and OH radical can damage blood vessel by forming various metabolites like peroxynitrite. Uric acid is involved in prevention of the formation of this product.. Recently Hink et alzzlrich Hink et aI, (2002) observed that certain mechanisms that maintain the endothelial function is mainly due to the prevention of degradation of super oxide by uric acid. And scavange the free radicals and reactive oxygen species. It help in production of NO levels. SOD3 is deactivated in the presence of H202 but uric acid blocks SOD inactivation and regenerates SOD3.

The above concept does not define the association between elevated uric acid levels and CVDs. As it may be as compensatory elevation of SUA to the elevated hypertension and heart disease. But it does not explain the concept why elevated SUA is associated with adverse outcomes. (Johnson, ET al2003).

An Antioxidant – Pro oxidant Urate Redox Shuttle:

These antioxidant mechanisms by uric acid can lead to pro oxidant in most of the conditions. (Bagnati, et. a1.1999; Patternson et al 2003). Hayden et al proposes interchange of antioxidant to pro oxidant in blood vessel that finally lead to atherosclerotic vessels.

In some studies they demonstrated that initial stages of the hypertension the uric acid act as antioxidant in blood vessel changes and also in atherosclerotic changes in blood vessels. (Nyyssonen, et al. 1997 but in late stages of SHT and atherosclerotic changes in blood vessel this antioxidant mechanism paradoxically changes to the pro oxidant mechanisms, ie, if SUA level exceed more than one third of normal range.

This uric acid and redox mechanisms mainly depend on its surrounding environment - the accelerated atherosclerotic vulnerable plaque in the intima, depleted of local antioxidants, with an increase in the oxidative stress, all those makes uric acid a pro oxidant.

Endothelial Dysfunction:

The several molecules are produced by the endothelium which is responsible of blood vessel inflammation, vascular tone, coagulation mechanisms, various remodeling changes in endothelium and new vessel formation. The production of NO synthase enzyme is the main mechanism in maintain homeostatsis in blood vessel wall.

This enzyme is most important mechanism in maintaining the blood veesel homeostasis and maintain the endothelium. The endothelium produces mainly ROS and super oxide ions due to the un coupling of the enzyme system in the endothelium.

The antioxidant pro oxidant urate redox is one of the causes of uncoupling of this enzyme system.

UA , proliferation of vascular smooth muscle cell and Inflammation:

As stated above the smooth muscle cell proliferation is activated by elevated uric acid levels.Uric acid stimulates rat smooth muscle cell proliferation in vitro. Uric acids enters smooth muscle cell by organs transporters. Inside the smooth muscle all it activates specific mitrogen activated protein kinases (Erk ½) with denovo induction of cyclo oxygenase , PDGFs, TXa2 formation.

UA plays an important role in production of MCP-1 in smooth muscle cell in rat blood vessels and it activates the p 38 MAP kinase and NF kappa b. Former involved in atherosclerotic changes in the blood vessels. NF kappa B also plays main role in pathogenesis of micro vessel disease. The UA also activates the production of the cytokines like IL-6 and TNF.

The potential risk factor for the cardiovascular disease is considered in hyperiuricemic patients if UA levels is more than 4 mg per deciliter and it considered as red flag. And all clinician should be involved in global risk reduction program in order to decrease the atherosclerotic process. (Melvin R Hayden 2004).

MATERIALS AND METHODS

Design of the study	CASE CONTROL STUDY
Period of the study	January 2016 to JUNE 2016
Ethical clearance	Applied for Ethical committee clearance
Consent	An informed consent will be obtained
Materials & Methods/ Selection of study subjects	Patients diagnosed with ESSENTIAL HYPERTENSION coming to Thanjavur medical college & hospital , who satisfy the inclusion criteria are subjected to detailed history, clinical examination, and investigations
Inclusion criteria	Patients who are diagnosed with ESSENTIAL HYPERTENSION Age 40 years or above and less than 70 years
Exclusion criteria	Secondary hypertension, Age <40 ;>70 years, Diabetes,IHD,CHF, gout , obesity , alcohol abuse, renal insuffiency, patient on cytotoxic drugs, low dose aspirin, thiazide diuretics
Analysis	The collected data will be analyzed using statistical package
Conflict of Interest	Nil
Financial Support	Nil
Participant's Principal Investigator	**DR. M. ELLANGOVAN** **MD (GENERAL MEDICINE) P.G**
Supervision and Guide	**Prof. Dr.GANESHAN, M.D. ,** **PROFESSOR AND HOD,** Department of General medicine, Thanjavur medical college & Hospital, Thanjavur

Inclusion Criteria:

- Patients with Essential hypertension
- Patients whose ages were above 25 years were included
- Both sexes were included.

EXCLUSION CRITERIA : Patients with

- Secondary hypertension .
- Age <40 ;>70 years.
- Diabetes, hypothyroidism, hyperparathyroidism.
- Ischemic heart disease, congestive cardiac failure.
- Gout.
- Alcohol abuse.
- Renal insufficiency, glomerulonephritis, pyelonephritis, hereditary nephropathy.
- Patients on Drugs – Levodopa, Ethambutol, Pyrazinamide, Nicotinic acid.
- Cytotoxic drugs , low dose aspirin,Thiazide diuretics

INVESTIGATIONS:

- Random blood sugar
- Serum lipid profile
- Blood urea , serum creatinine
- Serum uric acid
- ECG

Controls

Subject whose ages were above 25 years and had normal blood pressure and who met the above exclusion criterion.

Consent

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up after getting a written informed consent from them.

Materials

Thus a total of 165 cases that satisfied the inclusion and exclusion criteria above were taken up for subsequent study. 75 age and sex matched subjects were kept as control.

Limitations

1. In this study, both newly detected as well as known cases of essential hypertension that were on treatment were included in the study.
2. The study population included patients with essential hypertension both with and without target organ damage and other cardiovascular risk factors but without renal failure.
3. Only serum uric acid levels were analyzed. Urinary urate excretion and urate clearance was not done.

Methods

Selected Socio-demographic, clinical and laboratory data were elicited from the patients and controls and recorded in a master chart (enclosed in Annexure -Annexure-I)

I. Socio-demographic data

- Age
- Sex

II. Clinical data

- Body mass index
- Systolic and diastolic blood pressure
- Cardiovascular risk factors
- Clinical examination

III. Laboratory data

• **Blood Urea** Estimation done manually by using Diacetyl monoxime (DAM) technique.

•**Serum creatinine** Estimation was done using COBAS auto analyzer

• **Serum uric acid**

Enzymatic method (semi auto analyzer)

Principle:

Uric acid is converted by uricase to allantoin and hydrogen peroxide in the presence of peroxidase (POD) oxidises the chromogen to a red coloured compound which is read at 500 mm.

Uric acid + $2H_2O$ + O_2 Uricase Allantoin + CO_2 + H_2O_2

$2H_2O_2$ + 4 Aminoantipyrine + DHBS POD Red quinolone + H_2O + HCI

(DHBS - 3, 5 - Dichloro - 2 - Hydroxy benzene sulphonic acid).

DEFINITIONS USED IN THE PRESENT STUDY

1) Essential Hypertension

According to the JNC- VIII report, Hypertension is defined as systolic blood pressure of 140mm Hg and above and or diastolic blood pressure of 90 and above. In newly detected cases it was the mean of 3 seated right arm readings. The diagnosis that the hypertension is essential and not secondary was made on the over all clinical impression only. Laboratory investigations to rule out secondary causes were not done in each case.

2) Hyperuricemia

Hyperuricemia is defined as serum uric acid levels> 7mg/dl in males and >6mg/dl in females.

3) Over weight / Obesity.

- Over weight - Body mass index of ≥ 23
- Obesity - Body mass index> 25 (York et al)

4) Diabetes Mellitus

- Already a known case of diabetes mellitus on treatment
- Fasting plasma glucose ≥126mg/dl
- Two hour plasma glucose ≥ 200mg/dl

- Symptoms of diabetes plus random blood glucose $\geq$ 200mg/dl

5) Left ventricular hypertrophy

Based on electrocardiographic findings satisfying either Sokolon-Lyon criteria or Cornell voltye criteria (Sokolan, Lyon, 1949) (Casale, et al, 1987)

6) Hypertensive retinopathy

Based on Keith-Wagner-Barker grading

Grade I- attenuation of arteries. Grade II-arterio-venous nipping.

Grade III-with hemorrhage and exudates. Grade IV-with papiledema

RESULTS

This study group included total number of 165 subjects. Among these 165 subjects, 110 were cases (hypertensives) and 55 were controls (normotensives).

ANALYSIS OF CASES AND CONTROLS WITH RESPECT OF TO THE AGE

Table 1 Distribution of age among cases and controls

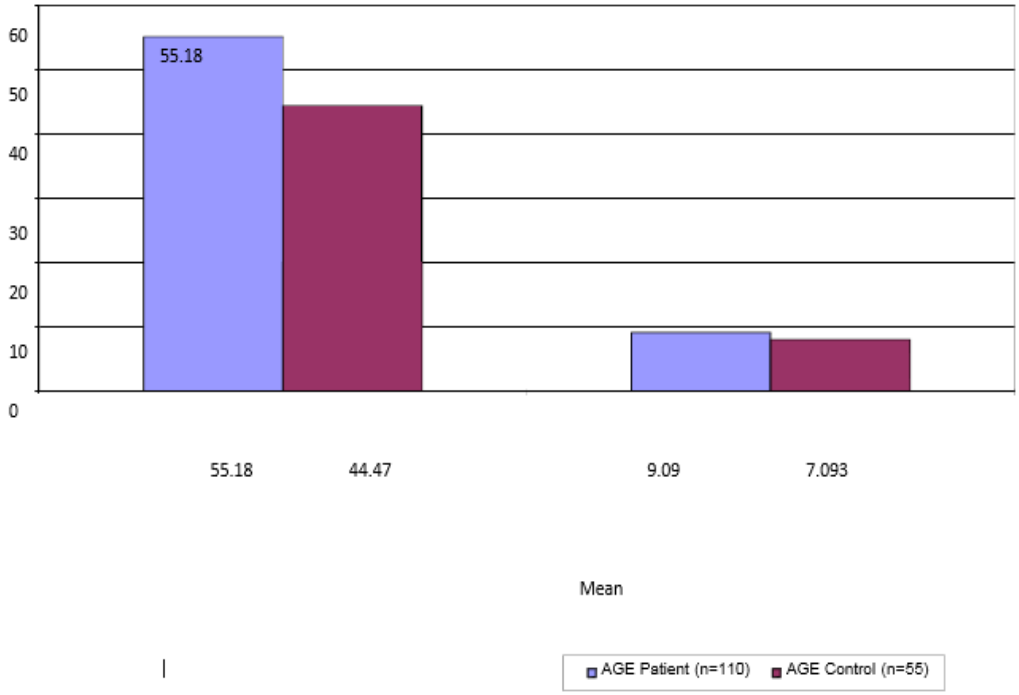
GROUP	**NO.**	**AGE**		**T TEST** **P V**ALUE
		MEAN	**S.D**	
CASES	**110**	**55.18**	**9.090**	
CONTROLS	**55**	**44.47**	**7.993**	**0.001**

The age of the subjects in this study group ranged from 26 to 79 years. The mean and standard deviation of age for cases and controls were

54.57 ±12.438 and 52.13 ±9.82 respectively.

There was significant (p value = 0.001) difference in the age composition of those with and without hypertension in this study. Hence elevated serum uric acid among cases and controls was dependent of age.

Distribution of age among cases and controls



SEX DISTRIBUTION IN THE STUDY POPULATION

Table 2 Distribution of study population in relation to gender

	CASES		CONTROLS	
	NO	PERCENTAGE	NO	PERCENTAGE
MALE	61	55.5	32	65.3
FEMALE	49	44.5	23	34.7
TOTAL	110	100	75	100

Among the 110 cases studied, there were 61 males and 49 females. Among the 55 controls, there were 32 males and 23 females. In the study population, 55.5% of males were hypertensives, while in females 44.5 % were hypertensives.

There was no significant (P-value= 0.139) difference in the sex distribution among cases and controls.

BMI	CASES		CONTROLS		T TEST (P VALUE)
	NO	%	NO	%	
< 23	34	30.9%	30	54.5%	0.119
≥23	76	69.1%	25	45.5%	
TOTAL	110		55		
MEAN	24.368		22.398		
S.D.	2.536		1.3472		

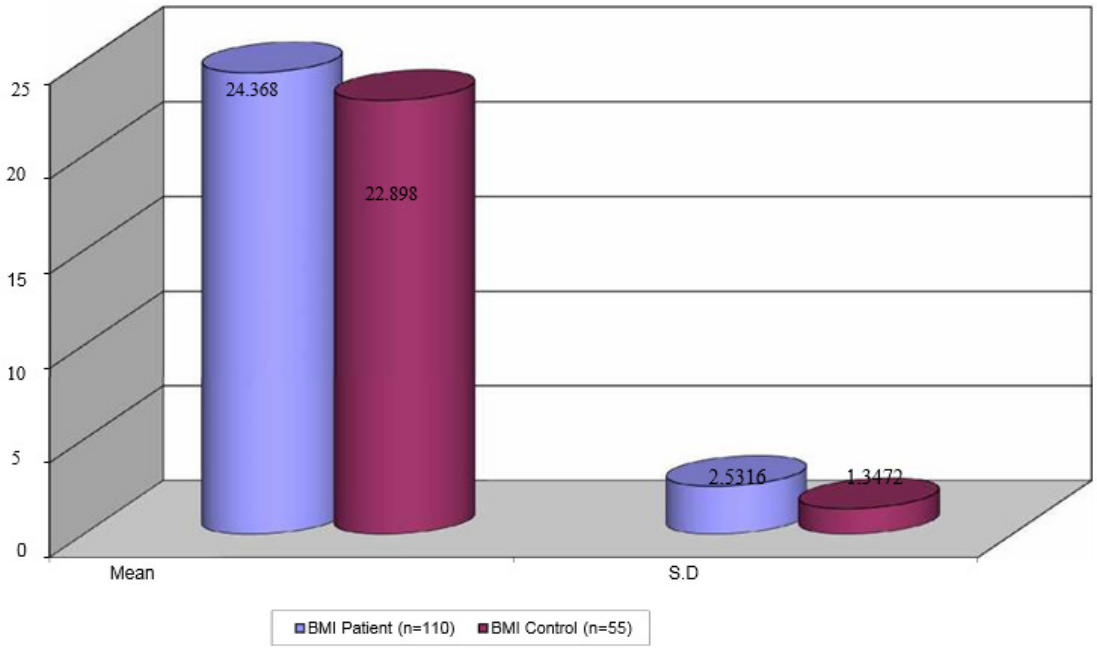
Table 3 BMI Distributions In The Study Population

ANALYSIS OF CASES AND CONTROLS WITH RESPECT TO BODY MASS INDEX (BMI)

The mean and standard deviation of BMI for cases and controls were 24.368±2.96 and 22.398±1.96 respectively. 40% of cases were obese while in the control group it was 10%.

The difference in Body Mass Index between cases and controls were statistically not significant (p-0.119).

BMI IN RELATION TO SERUM URIC ACID IN STUDY GROUP

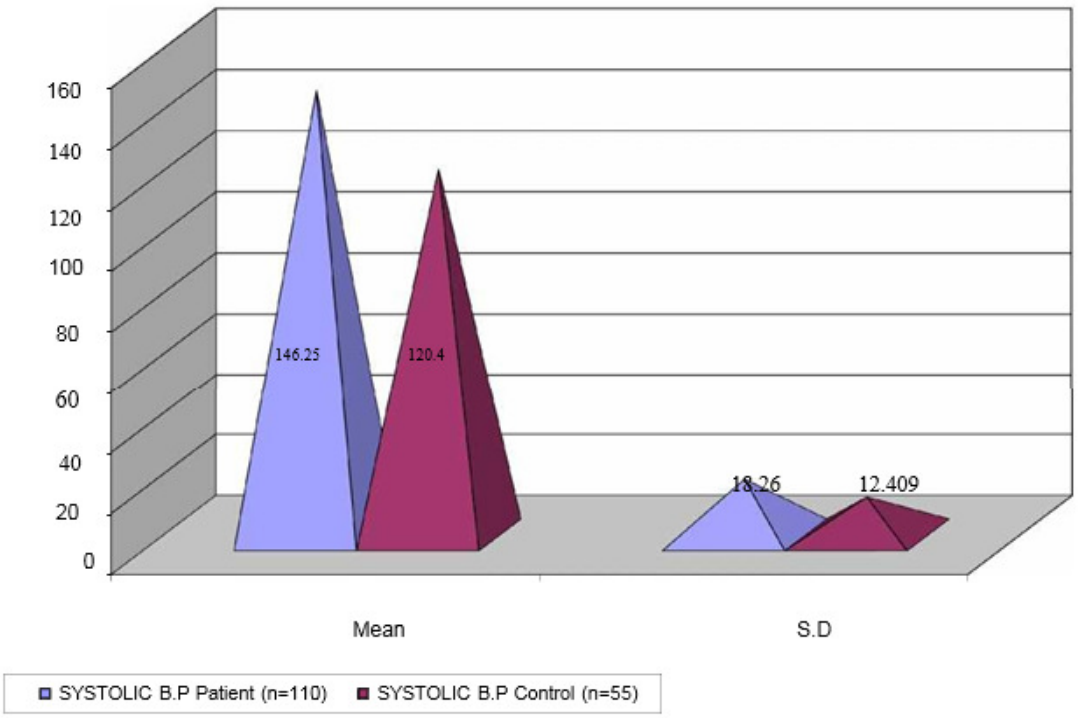


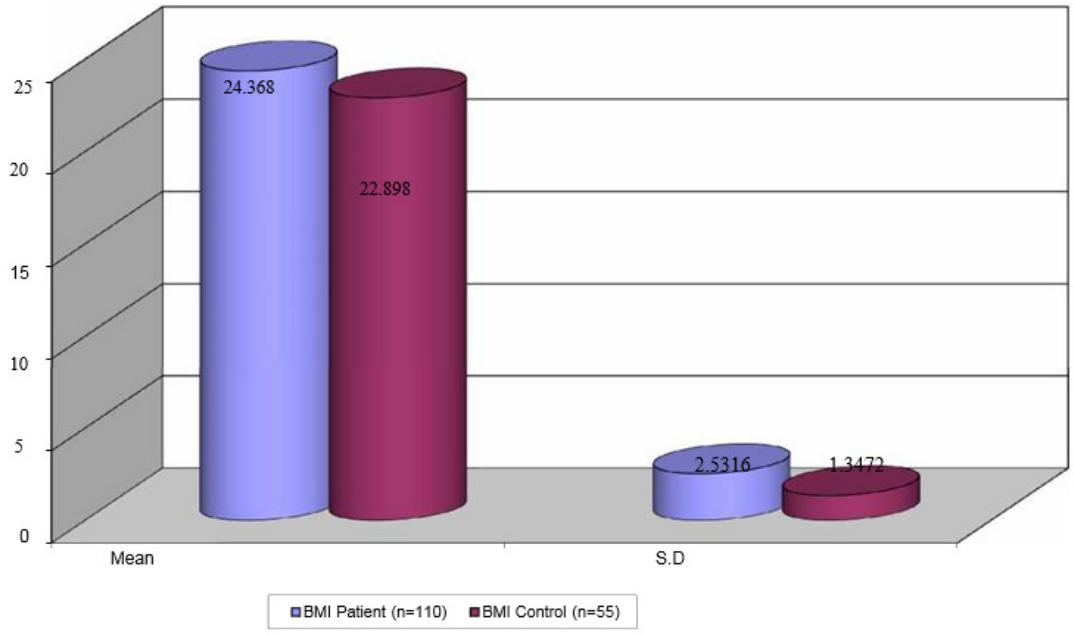
DISTRIBUTION AMONG CASES AND CONTROLS

Table 4 Distribution of systolic and diastolic BP among study group

Blood Pressure	**Group**	**No**	**Mean**	**S.D**
SYSTOLIC BP	CASES	110	146.25	18.266
	CONTROLS	55	120.40	12.409
DIASTOLIC BP	CASES	110	86.82	8.232
	CONTROLS	55	75.67	8.501
PULSE PRESSURE	CASES	110	59.43	1.326
	CONTROLS	55	44.73	1.811

The mean and standard deviation of systolic and diastolic BP in cases were 146.25±16.92 and 86.68±8.95 respectively.


160
140
120
100
80
60
40
20
0
146.25
120.4
18.26
12.409
Mean
S.D
SYSTOLIC B.P Patient (n=110)
SYSTOLIC B.P Control (n=55)


25
20
15
10
5
0
24.368
22.898
2.5316
1.3472
Mean
S.D
BMI Patient (n=110)
BMI Control (n=55)

DISTRIBUTION OF CASES AND CONTROLS IN RELATION TO CARDIOVASCULAR RISK FACTORS

In this study population family history of cardiovascular disease, smoking were equally prevalent in both cases and controls.

Table 5 Distribution of study population in relation to cardiovascular risk factors.

Family History H/O CVD	**Patient**	**percentage**	**Control**	**Percentage**	**Total**	**Percentage**	
No	80	72.7%	39	70.9%	119	72.1%	X^2=0.060 Df=1 .806>0.05 Not Significant
Yes	30	27.3%	16	29.1%	46	27.9%	
Smoking							
No	84	76.4%	41	74.5%	125	75.8%	X^2=0.066 Df=1 .797>0.05 Not Significant
Yes	26	23.6%	14	25.5%	40	24.2%	

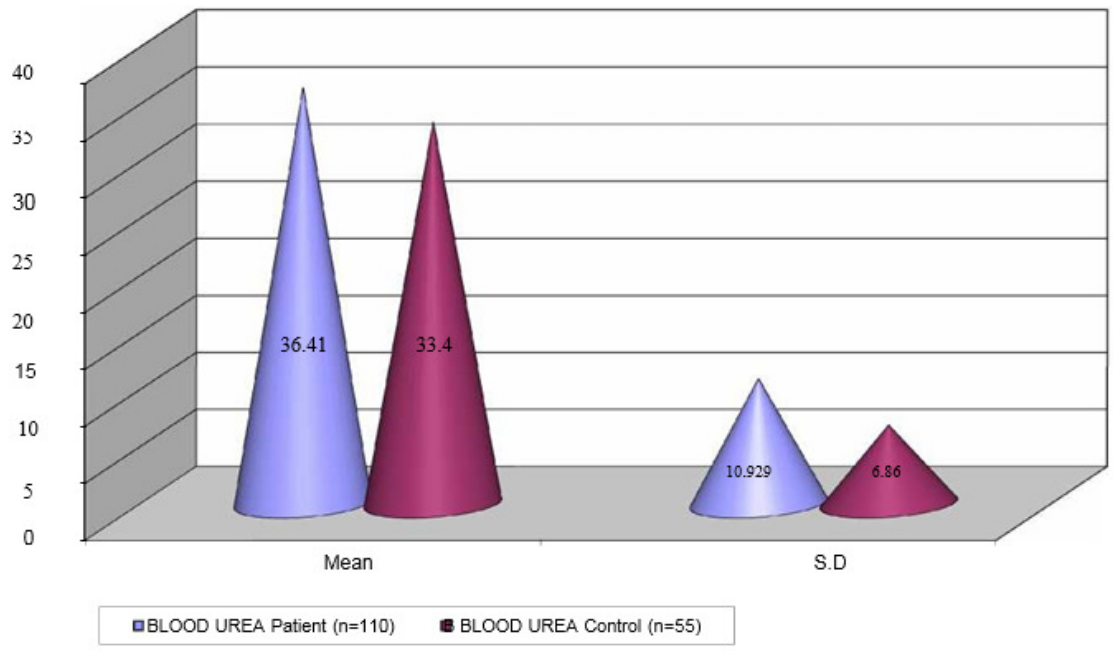
There was no statistical significance between cases and controls in relation to family history of cardiovascular disease, smoking .

Distribution of cases and controls in relation to blood sugar,urea and serum Creatinine.

Table 6 Distribution of study population in relation to blood parameters

		NO.	**MEAN**	**SD**	**P**
BL.SUGAR	CASES	110	113.81	28.930	0.065
	CONTROLS	55	101.80	19.525	
BL.UREA	CASES	110	36.41	10.929	0.064
	CONTROLS	55	33.40	6.080	
SR.CREAT	CASES	110	1.060	0.3693	0.129
	CONTROLS	55	0.973	0.2940	

There was no statistical significance in distribution of cases and controls in relation to Blood sugar, urea and serum creatinine.


40
35
30
25
20
15
10
5
0
36.41
33.4
10.929
6.86
Mean
S.D
BLOOD UREA Patient (n=110)
BLOOD UREA Control (n=55)

ANALYSIS OF CASES IN RELATION TO TARGET ORGAN DAMAGE (TOD)

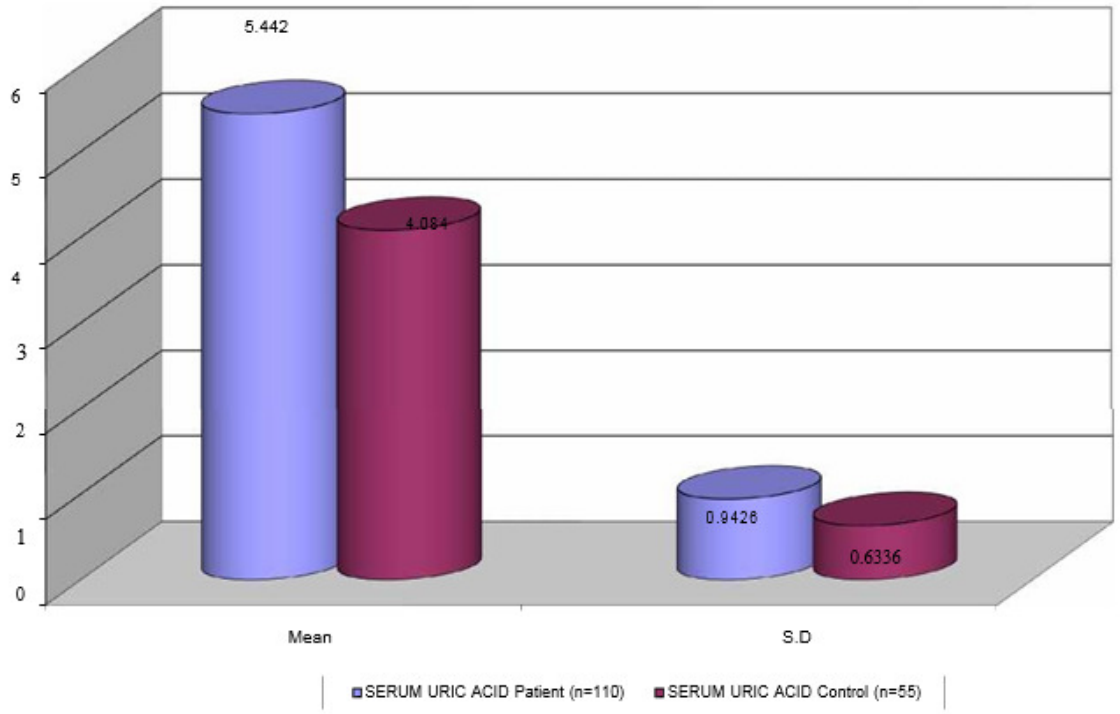
The details of prevalence of target organ damage (TOD) - Left ventricular hypertrophy (LVH), Coronary artery disease (CAD), Congestive cardiac failure (CCF), Cerebrovascular accident/Transient ischemic attack (CVA/TIA).

Table 7 Distribution of cases in relation to TOD

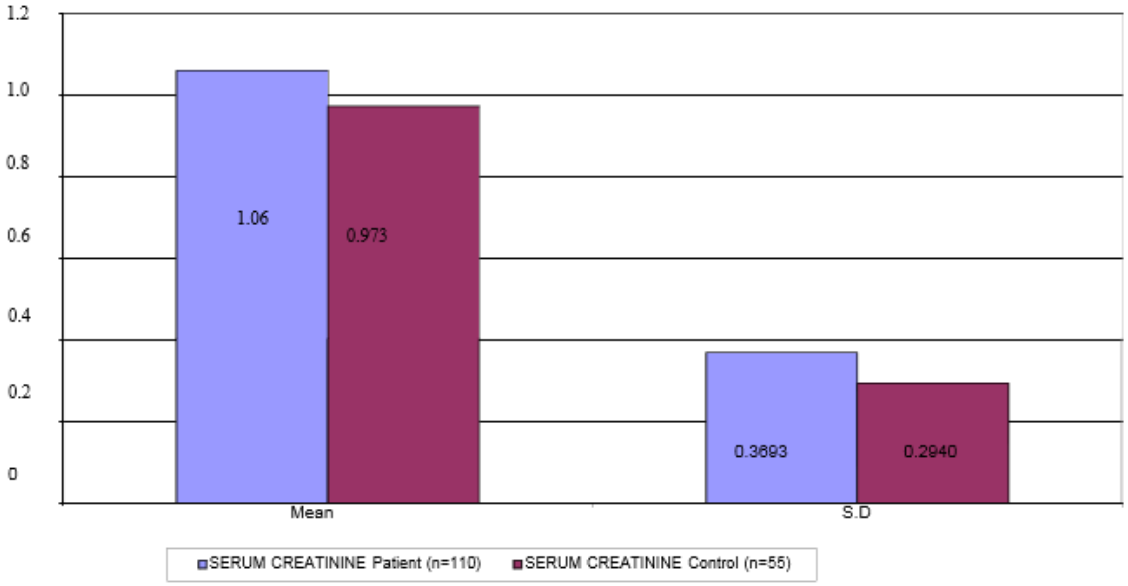
TOD		Cases	
		No.	Percentage
LVH	Present	23	20.9
	Absent	87	79.1
CAD	Present	46	41.8
	Absent	64	58.2
CVA	Present	19	17.3
	Absent	91	82.7
	Grade III	2	1.3

Among 110 cases, LVH was present in 23 cases, CAD was present in 46 cases, CVA was present in 19 cases.

SERUM URIC ACID IN RELATION TO STUDY GROUP



SERUM URIC ACID IN RELATION TO SERUM CREATININE IN STUDY GROUP



DISTRIBUTION OF CASES AND CONTROLS IN RELATION TO SERUM URIC ACID

Table 9 Comparisons of mean uric acid levels among the cases and controls

	Group	No.	Mean	SD	P-value
SR.URIC ACID	CASES	110	5.442	0.9426	0.0001
	CONTROLS	55	4.084	0.6336	

Serum uric acid in cases varied from 3.1mg% to 7mg% and in the control from 2.8mg% to 5.9mg%. The mean and standard deviation of serum uric acid among cases were 5.442±1.31 while in control it was 4.084±0.7 respectively. This table clearly shows that the serum uric acid level was significantly influenced by systemic hypertension.

Hyperuricemia is defined as serum uric acid levels >7mg/dl in males and >6mg/dl in female. 16 cases had hyperuricemia while none of the controls had hyperuricemia. Mean and SD of hyperuricemia in cases 6.5±0.67. Hyperuricemia was present in 14%of hypertensives.

This table clearly shows hyperuricemia was statistically significant in hypertensives when compared to normotensives

SEX DISTRIBUTION OF SERUM URIC ACID IN STUDY POPULATION

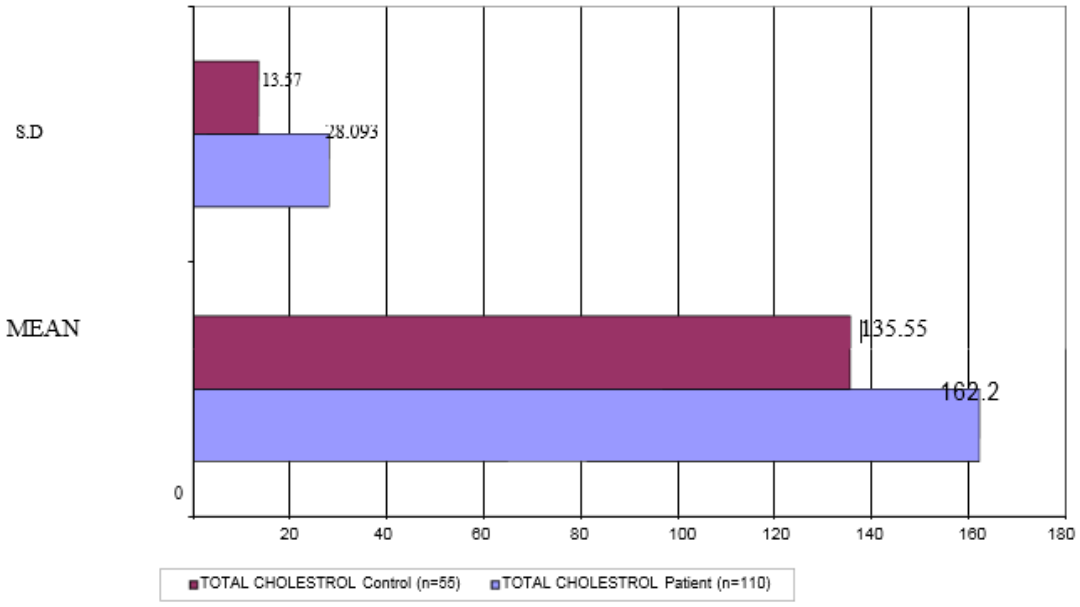
Table 10 Comparision Of Uric Acid Levels Amongs the Study Groups

GROUP	SEX	N	SR URIC ACID		P VALUE
			MEAN	SD	
CASES	FEMALES	49	5.734	1.1036	.191
	MALES	61	5.236	.7338	
CONTROLS	FEMALES	22	4.3409	.6768	
	MALES	32	4034	.6067	

The mean serum uric acid level in hypertensive males and females were 5.236±1.33 and 5.734±1.26 respectively.

Even though the mean serum uric acid level was higher in hypertensive females when compared to hypertensive males it was not statistically significant.

SERUM URIC ACID IN RELATION TO SERUM CHOLESTROL IN STUDY GROUP



SERUM URIC ACID IN RELATION TO BODY MASS INDEX

In the study population, BMI <23 was seen in 64 cases among 101 subjects, and the mean serum uric acid level was 4.827±1.4. BMI ≥23 was seen in 76 cases among 110 subjects and and the mean serum uric acid level was 5.407±1.18.

Table No-11: Relationship Between BMI and Uric Acid Level in cases and controls

	Study Group	Serum uric Acid			Cases	Serum uric Acid		
BMI	No.	Mean	S.D	PVALUE	No.	Mean	S.D	pVALU
<23	64	4.827	1.1335		34	5.521	1.033	
≥23	101	5.092	1.0122	0.119	76	5.407	.9040	0.560

This table shows Body Mass Index was not significantly influencing the serum uric acid. Pvalue (0.560)

Table 12 Serum uric acid Levels in relation to smokers in study population

			H/o Smoking	
			Absent	**Present**
Serum Uric Acid	Normal	Count	117	32
		Percentage	93.6%	80%
	Hyperuricemia	Count	8	8
		Percentage	6.4%	20%

		Serum uric acid		
H/o smoking	No.	Mean	S.D.	pValue
YES	40	4.867	1.0369	0.828
NO	125	5.028	1.0756	

This table showed smoking did not influence serum uric acid level significantly.

Hyperuricemia was present in 24% of smokers in study population. The mean serum uric acid level of smokers in study population was 4.867 ±1.3 when compared to non smoker 5.083±1.03.

Serum uric acid level in relation to Target Organ Damage (TOD)

The mean values and standard deviation of target organ damage which was present in cases were shown in table below.

Table 13 Serum uric acid level in relation to target organ damage.

TOD		**No.**	**Mean**	**S.D.**	**P-value**
LVH	YES	23	5.387	0.9172	0.755
	NO	87	5.456	0.9539	
CAD	YES	46	6.024	.8935	0.001
	NO	64	5,023	.7361	
CCF	YES	19	5.074	.9774	0.061
	NO	91	5.519	.9222	

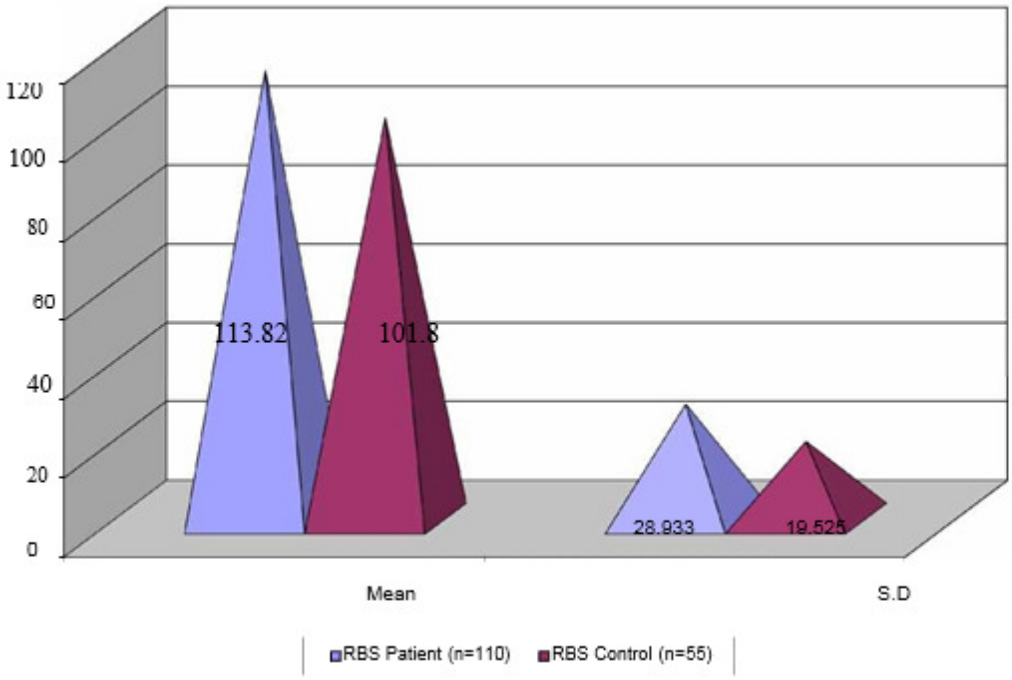
Coronary arterial disease was seen in 46 hypertensive individuals. The mean serum uric acid level in cases with CAD was 6.024±0.02 while it was 5.023±0.01 among the cases without CAD. There was significant difference noticed among the cases with and without CAD (P-value 0.01). There was no significant difference noticed among the cases with and without other target organ damages like LVH, CVA.

Serum uric acid level in hypertensive subjects with and without Target Organ Damage (TOD).

Table 14 Serum uric acid level in cases with/without TOD

TOD	No	Mean	S.D	P-value
Present	88	5.650	1.0171	0.002
Absent	22	5.078	.6627	

The mean serum uric acid level in hypertensive subjects with and without TOD was 5.650±1.4 and 5.078±0.93 respectively. The serum uric acid level in cases with and without target organ damage was not statistically significant(P-value0.701)


120
100
80
60
40
20
0
113.82
101.8
28.933
19.525
Mean
S.D
RBS Patient (n=110)
RBS Control (n=55)

DISCUSSION

Hypertension is the most common form of cardiovascular disease which is present in nearly 25% of adults and the prevalence increases with age. Hypertension is strongly associated with hyperuricemia (Hayden, 2004). Elevated UA levels is detected in more than thirty percent of individuals as observed by cannon (1966).

In this study the relation between serum uric acid level and hypertension was analyzed. Previous strong epidemiological data had linked serum uric acid level and hypertension (Cannon et al 1966, Kinsley et al, 1961, Klein et al, 1973) and experimental animal data suggested hyperuricemia causes hypertension (Mazzali et al 2001, Sanchezs et al 2002, Watanable, 2002).

Among the 110 cases of hypertension, hyperuricemia was seen in 16 cases, which is account for 14% of cases. Cannon et al 1966 showed a prevalence of hyperuricemia in 25% of untreated hypertensive cases. But in our study many of the cases were on treatment which might have affected the results.

The kidney changes like preglomerular changes due to elevated SUA levels is observed by several studies independent of systemic hypertension (Mazzali et al 2001) and once vascular disease was established, the hypertension was driven by kidney and lowering uric acid level was no longer protective (Watanable, 2002)

The observation from the Framingham study revealed that the correlation of uric acid level with blood pressure was attenuated in the study population as they aged is consistent with these data. (Source : Feig and Johnson 2003).

Various studies have linked the development of hypertension with hyperuricemia. The Olivetti heart study (Joss et al, 1994) has shown an independent positive association between serum uric acid and development of hypertension. Selby, et al, (1990) have concluded in their study that both forced vital capacity and serum uric acid were closely linked to the development of hypertension.

Feig and Johnson et al (2003) found that serum uric acid was elevated in 89% of children with essential hypertension. He concluded that serum uric acid level directly correlated with blood pressure in untreated children and that a serum uric acid level of >5.5mg% in an adolescent being evaluated for hypertension strongly suggests essential hypertension.

The mean age for cases in this study is 54.57 years. This might explain the lower prevalence of hyperuricemia when compared with Feig and Johnson et al study (2003).Serum uric acid values were correlated with various variables that affected the target organ damage in hypertensive population. In study groups, BMI and sex did not have any significant effect on the uric acid levels. Among the Athens study group, there was a positive correlation between SBP and serum uric acid values where as in our study and Italian study, the correlation of SBP and serum uric acid levels was not significant. However we will have to emphasize the fact that target organ dysfunction primarily depends on adequacy of blood pressure control. This has been emphasized by previous studies by Francesca et al.

The role of increased pulse pressure in the context of cardiovascular risk assessment and stratification is currently receiving growing attention. Furthermore, elevated pulse pressure values, measured both in office and by 24-hr ambulatory monitoring, have been linked to the presence of sub-clinical cardiovascular damage, i.e. left ventricular hypertrophy, increased carotid wall thickness and microalbuminuria as well as to structural changes in peripheral vasculature. It has been suggested that high pulse pressure levels reflect the degree of stiffness of the arterial tree, regardless of whether they are caused by increased systolic blood pressure (SBP) and/or reduced diastolic blood pressure (DBP).

In our study, it has been noted that serum uric acid levels did not correlate significantly with BMI suggesting SUA as an independent marker of cardiovascular and renal abnormalities. Similarly in the Italian study, total cholesterol did not correlate significantly with serum uric acid. But BMI correlated significantly with serum uric acid values in both Italian and Athens study.

Further in our study there was a significant correlation of serum uric acid levels with target organ dysfunction such as cardiovascular diseases. These findings were similar to the Italian study, which also reported a strong association between serum uric acid levels and pre-clinical organ dysfunction. In the Athens study, there was a s ignificant correlation with SUA and cardiovascular diseases.

There is pathophysiological role in relationship between SUA and cardiovascular morbidity and mortality in un treated hypertensive patients. In our study there significant co relation between the cardiovascular event and elevated SUA level and it proves to be the major risk assessment in estimation of major events.

The mean serum uric acid level in male is 5.734±1.33 while in female it is 5.236±1.26 and the difference is not statistically significant. This is in contrast with the study done by Ketker et al (1979) in which they have shown that the serum uric acid level was more in males when compared to females.

In this study serum uric acid do not correlate with Body Mass Index. The mean serum uric acid level in hypertensive with BMI<23 and BMI≥23 are 5.521mg/dl and 5.407mg/dl and the difference is not statistically significant. Shobha Kelker et al and Healey have shown in their study that there was no significant correlation between serum uric acid level and obesity.

The serum uric acid level is significantly higher in hypertensives when compared to normotensive subjects. The mean serum uric acid level in cases is 5.442mg/dl while in the control it is 4.084mg/dl. This is consistent with other studies, which has shown serum uric acid is elevated in hypertension.

In a review article by Hayden et al (2004) it was noted that elevation of serum uric acid level >4mg/dl should be considered as a **red flag** in those cases with risk for cardiovascular disease.

In this study 76%of hypertensive has serum uric acid level >4mg/dl, while in controls 40% of subjects have serum uric acid level >4mg/dl. In these subjects the clinicianshould strive to utilize global risk reduction programme to reduce the complications of atherogenic process. The details in relation to this study are shown in the table given below.

There are many mechanisms between the elevated UA levels and heart disease and progression of hypertension that include : (1) elevated UA synthesis to reduce the oxidative mechanisms and counteract the damage in the blood vessels like atherosclerosis. (2) the progression of SHT and decreased GFR due to decreased clearance in the kidneys. The association between the elevated SUA and heart diseases were involved in many studies as anti-hypertensive has capability to reduce the moderate changes in the SUA levels , which could explain their ability to protect the cardiovascular system and kidneys. In conclusion the present study showed that elevated SUA is predictable marker of preclinical CVDs in a population of patients with essential hypertension.

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century (Gertler et al, 1951). However, its role as a cardiovascular risk factor remains controversial.

The Framingham heart study concluded that uric acid does not have a causal role in the development on coronary heart disease and death from other cardiovascular disease. In an epidemiologic follow up study an association between serum uric acid and cardiovascular disease was shown (Fredman et al). The recent PIUMA study also concluded that raised serum uric acid is a powerful risk factor for subsequent cardiovascular disease and all cause mortality (PaolaVerdecchia,et al,2000).

A large body of evidence links uric acid with the metabolic syndrome of insulin resistance, obesity, hypertension and dyslipidemia. Cappuccio et al reported an association of hyperuricemia with increased renal tubular sodium reabsorption, thus providing a link with hyperuricemia, hypertension and hyperinsulinemia. There is association of serum uric acid with increased cholesterol. Smoking which is also a cardiovascular risk factor does not significantly influence serum uric acid level in the present study. (Hypertension. 2005; 45:991-996)

In our study we concluded that uric acid level in patients with TOD is significantly elevated compared with those without TOD .In our study, the serum uric acid level in cases with and without target organ damage is statistically not significant (P-value0.002)

Adenosine synthesis and release are up regulated in response to hypoxia and tissue ischemia. The adenosine is rapidly degraded by endothelium to uric acid. Therefore hyperuricemia is considered as a marker of underlying tissue ischemia (Waring et al2000).

The Subjects with altered Coronary Flow Rate (CFR) had significantly higher SUA levels compared with those with normal CFR These results support a role for SUA level as an independent marker of target organ damage in hypertension (Mustafa Caliskan, Dogan Erdogan et al).

Serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality (JAMA. 2000; 283:2404-2410).

In our study, coronary arterial disease is seen in 53 hypertensive individuals. The mean serum uric acid level in cases with CAD is 6.024±0.02 while it is 5.023±0.01 among the cases without CAD. There is significant difference noticed among the cases with and without CAD (Pvalue- 0.01).

Hyperuricemia, a known correlate of oxidative stress, is a marker for adverse prognosis among individuals with heart failure. Hyperuricemia is a novel, independent risk factor for heart failure in a group of young general community. This has implications for development of preventive strategies for heart failure (Circulation: Heart Failure. 2009; 2:556-562)

As there are controversies with reference to elevated uric acid as an independent risk factor for cardiovascular disease, it is suggested to carry out similar prospective studies among newly detected hypertensive population and follow them to ascertain truth.

CONCLUSION

1. Hyperuricemia (>7mg/dl in males and >6mg/dl in females) is found in 14% of hypertensives while none of the normotensives had hyperuricemia.

2. Serum uric acid level is significantly elevated in Essential hypertension.

3. There is no correlation between serum uric acid with gender , body mass index, smoking.

4. Serum uric acid level is significantly elevated in cases with coronary artery disease as compared to those with other target organ damage.

5. In our study the ninety percent of hypertensive population had SUA level more than four mg per deciliter which is now concluded as ":red flag" in those with risk factor for cardiovascular disease.

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PROFORMA

NAME: AGE: SEX: IP/OP No:

CAD:

CVA/TIA: HISTORY OF SMOKING: FAMILY HISTORY:

EXAMINATION:

BLOOD PRESSURE: ALL PERIPHERAL PULSES: CCF:

CVA/TIA:

INVESTIGATIONS: ECG:

BL.SUGAR: BL.UREA: SR.CREATININE: SR.URIC ACID:

ABBREVIATIONS

BMI:Body Mass Index.

S.H.T : Systemic hypertension

S.B.P:Systolic blood pressure.

D.B.P:Diastolic blood pressure.

FAMILY.H: Family history.

DM:Diabetes mellitus.

LVH:Left ventricular hypertrophy.

CAD:Coronary artery disease.

CCF:Congestive cardiac failure.

CVA:Cerbrovascular accident.

TIA:Transient ischemic attack.

RBS:Random blood sugar.

BL.UREA:Blood urea.

Scr:Serum creatinine.

SUA:Serum uric acid.

U.A; Uric acid

M.I : Myocardial infarction

B.P; Blood pressure

PVDs: Perpheral vascular diseases

NA+ ; Sodium

NACL; Sodium chloride

GFR; glomerular filtration rate

CO; cardiac output

RAAS ; Renin angiotensinogen system

CVDs; Cardiovascular diseases

ABPI; Ankle brachial pressure index

S.NO	AGE	SEX	BMI	SYSTOLIC B.P	DIASTOLIC BLOOD PRESSURE	FAMIY HISTORY H/O CVD	SMOKING	LVH	CAD	CVA	BLOOD UREA	SERUM CREATININE	RBS	TOTAL CHOLESTROL	SERUM URIC ACID
1.	60	M	27.7	150	80	Y	Y	Y	N	N	43	1.2	81	157	5.2
2.	65	F	21.4	160	90	Y	N	N	Y	N	33	1.0	89	227	7.9
3.	62	F	26.6	150	100	N	N	N	N	N	32	0.8	69	188	4.9
4.	65	M	28.7	140	100	N	Y	N	Y	N	37	1.3	134	183	5.3
5.	70	F	20.7	150	90	N	N	Y	Y	N	36	1,1	76	194	7.2
6.	51	M	19.9	170	90	N	Y	N	Y	N	35	1,6	187	141	6,4
7.	46	F	27.3	150	80	N	N	N	N	N	41	1.0	88	128	5.3
8	48	M	27,8	170	90	N	Y	N	N	N	70	1.2	118	167	4.9
9.	55	M	40.5	160	80	N	Y	N	Y	N	38	1,3	116	130	6.4
10.	55	M	21.2	170	80	N	Y	Y	Y	N	42	0.8	134	186	6.8
11.	72	F	26.6	156	80	N	N	N	Y	N	45	2.4	174	175	5.3
12.	68	F	25.5	160	100	N	N	N	Y	N	92	1.1	88	157	9.0
13.	60	F	26.7	170	80	N	N	N	N	N	82	1.2	70	254	5.5
14.	48	F	22.3	150	70	N	N	N	Y	N	32	0.7	112	131	8.2
15.	60	F	22.6	170	70	N	N	N	N	N	43	1.7	93	146	4.7
16.	64	M	25.4	180	90	N	Y	Y	N	Y	32	0.8	95	153	5.3
17.	56	F	26.2	140	100	N	N	N	Y	Y	42	0.9	78	159	6.3
18.	62	M	22.6	160	100	N	Y	N	Y	Y	34	1.0	98	149	5.7
19.	48	F	27.3	150	80	N	N	N	N	N	35	0.8	123	201	4.9
20.	57	M	23.8	160	90	N	N	N	N	N	32	0.8	174	171	4.4
21.	42	F	22.4	130	90	N	N	N	N	N	35	0.9	89	261	5.5
22.	52	F	27.0	150	80	Y	N	N	N	N	32	0.7	106	187	4.9
23.	57	F	22.5	140	100	Y	N	N	N	N	35	1.0	83	144	5.1
24.	51	F	24.7	160	90	N	N	Y	N	N	34	0.8	82	167	5.2
25.	47	M	26.2	150	100	N	N	N	N	Y	51	0.8	95	179	6.1

26.	42	F	27.3	150	90	N	N	N	N	N	41	0.9	130	172	4.4
27.	67	M	22.2	146	90	N	N	N	Y	N	31	0.9	140	180	5.7
28.	68	M	20.3	130	90	N	N	N	N	N	36	1.0	134	184	4.6
29.	56	F	26.2	140	90	N	N	N	Y	N	37	1.0	142	201	6.3
30	50	M	25.5	140	80	N	N	Y	N	N	38	0.9	118	176	5.2
31	70	F	21.1	154	90	N	N	Y	N	N	38	0.9	134	182	5.0
32	56	M	23.2	110	70	N	N	Y	N	N	39	1.1	156	194	5.4
33	62	F	24.4	150	90	N	N	N	N	N	38	1,3	113	142	5.1
34	43	M	25.6	140	90	N	N	Y	N	N	37	1,0	174	163	6.3
35	56	M	23.2	130	80	N	N	Y	N	N	32	1.2	89	172	5.6
36	64	F	27.2	190	80	N	N	N	Y	N	30	1.0	106	220	6.5
37	68	M	22.4	149	90	N	Y	N	Y	Y	72	2.8	83	146	6.3
38	42	M	23.1	110	70	N	Y	N	Y	N	27	0.9	82	123	5.7
39	63	M	25.5	140	90	N	Y	Y	Y	Y	43	1.2	95	126	4.4
40	58	M	22.5	130	90	Y	Y	N	Y	N	34	1.0	130	152	6.0
41	55	F	23.4	120	90	Y	N	Y	Y	N	39	1.3	140	143	6.1
42	49	m	25.4	140	90	Y	N	N	N	Y	31	1.0	134	170	5.2
43	52	M	24.5	120	90	Y	N	N	N	Y	34	1.0	142	180	4.0
44	48	M	23.2	150	90	Y	N	N	N	Y	44	1.0	118	179	6.1
45	52	M	24.6	160	90	Y	N	N	N	N	33	0.8	134	154	4.4
46	55	M	22.5	180	90	Y	N	N	N	N	31	1.0	156	191	5.9
47	50	M	24.4	170	90	Y	N	N	N	N	32	0.7	113	185	4.9

48	66	M	25.2	140	90	Y	N	N	N	N	38	0.7	174	160	6.0
49	66	M	22.3	150	90	N	N	N	N	N	32	0.8	99	156	4.6
50	70	F	22.0	110	70	N	N	N	N	N	33	0.8	102	155	5.2
51	46	M	24.3	140	90	N	Y	N	N	N	34	0.9	86	156	4.6
52	55	F	25.2	130	90	N	N	N	Y	N	33	O.9	110	131	6.4
53	53	M	23.4	130	90	N	Y	N	N	N	31	0.6	89	187	6.2
54	59	M	22.6	120	90	N	Y	Y	Y	N	33	1.0	77	180	6.3
55	66	F	25.2	140	90	N	N	N	Y	N	32	1.0	92	165	6.6
56	45	F	26.2	130	80	Y	N	N	Y	N	42	0.9	98	134	5.8
57	80	M	23.4	180	90	N	N	N	Y	N	28	0.8	87	112	5.5
58	60	M	25.5	140	90	Y	N	Y	Y	N	34	1.2	66	145	5.5
59	50	F	22.4	120	80	N	N	N	Y	N	36	0.9	75	209	5.8
60	56	F	22.6	130	90	N	N	Y	N	N	27	1.0	77	103	3.5
61	48	F	27.7	150	90	N	N	N	N	Y	23	1.1	74	156	3.5
62	52	F	22.4	170	80	N	N	Y	N	N	36	1.0	73	147	3.6
63	63	M	26.2	150	90	N	N	N	N	Y	32	1.1	99	176	4.5
64	45	M	23.4	140	80	Y	N	Y	N	N	33	0.8	112	165	5.2
65	60	M	23.2	130	70	N	Y	N	N	N	37	1.2	142	125	3.8
66	65	F	25.2	180	90	N	N	N	N	N	26	1.3	133	143	4.6
67	44	M	22.1	160	100	N	Y	N	N	Y	25	1.0	154	162	4.3
68	61	F	22.5	170	90	N	N	N	N	N	28	1.2	124	132	4.5
69	63	M	26.2	140	90	N	N	N	N	N	29	1.0	141	148	4.6

70	50	F	25.5	140	80	N	N	N	N	N	38	0.9	118	176	5.3
71	70	M	21.1	140	90	N	N	Y	Y	N	38	0.9	134	182	5.5
72	56	M	22.2	110	70	N	N	N	Y	N	39	1.1	156	194	5.5
73	62	F	24.4	150	90	N	N	Y	Y	N	38	1,3	113	142	5.2
74	43	M	23.3	140	80	N	N	N	N	N	37	1,0	92	163	6.4
75	56	M	23.2	160	80	Y	N	N	Y	N	32	1.2	88	172	5.8
76	64	M	27.2	180	90	Y	N	Y	Y	N	30	1.0	112	226	6.6
77	68	F	25.5	149	90	N	N	N	Y	N	72	2.8	162	136	6.2
78	42	M	24.2	120	70	N	N	N	Y	N	27	0.9	124	123	5.9
79	63	F	25.5	140	80	N	N	N	Y	N	43	1.2	132	142	4.2
80	58	F	20.3	130	90	N	N	N	Y	N	34	1.0	125	152	6.1
81	55	F	23.4	140	90	N	N	N	Y	N	39	1.3	116	143	5.7
82	49	M	21.4	140	90	N	Y	N	N	N	31	1.0	87	170	5.4
83	52	F	24.5	130	90	N	N	N	N	N	34	1.0	92	180	4.1
84	48	F	23.2	170	90	N	N	N	N	N	44	1.0	90	179	6.5
85	52	M	24.6	170	90	N	N	Y	N	Y	33	0.8	91	154	4.2
86	65	M	25.4	140	90	Y	N	N	N	N	32	0.7	174	146	4.1
87	43	F	26.2	154	80	N	N	N	N	N	30	1.0	89	123	5.2
88	32	M	22.6	130	100	N	N	N	N	Y	65	0.8	106	126	4.3
89	40	M	27.3	170	90	N	N	N	N	N	35	0.8	83	152	6.4
90	38	F	23.8	150	100	N	N	N	Y	N	24	0.9	82	143	5.8
91	35	F	22.4	150	80	Y	N	N	N	N	35	0.9	95	180	5.2

92	48	F	27.0	146	80	Y	N	N	N	N	39	1.0	130	170	5.4
93	52	M	26.2	130	70	Y	Y	N	N	N	41	1.0	140	149	5.1
94	57	F	25.5	154	90	Y	N	N	Y	N	34	0.9	134	153	6.4
95	47	M	21.1	110	80	N	N	N	Y	N	37	0.9	142	124	5.5
96	42	F	23.2	150	100	N	N	N	N	Y	32	1.1	118	164	6.3
97	38	F	24.4	140	90	N	N	N	N	N	30	1,3	134	134	5.4
98	52	M	25.6	130	60	N	N	N	N	N	24	1,0	156	123	5.5
99	55	M	23.2	190	90	Y	Y	N	Y	Y	27	1.2	113	153	4.2
100	56	M	27.2	149	80	Y	Y	N	N	N	28	1.0	174	155	4.1
101	44	M	22.4	110	70	Y	Y	N	N	N	32	2.8	89	164	5.5
102	61	M	23.1	140	90	Y	Y	N	N	Y	29	1.0	106	172	4.1
103	68	M	25.5	130	90	N	Y	N	Y	N	31	1.0	83	220	6.3
104	52	F	22.5	120	90	N	N	Y	N	N	34	0.9	82	146	5.2
105	50	M	23.4	140	90	N	N	N	Y	N	32	0.8	95	123	5.0
106	58	M	25.4	120	90	Y	Y	Y	Y	N	23	1.2	130	126	5.4
107	60	M	22.6	150	90	Y	Y	N	N	Y	29	0.9	140	152	5.1
108	50	M	27.2	160	90	Y	N	N	Y	N	31	1.0	134	143	6.3
109	59	F	22.2	150	90	N	N	N	Y	N	25	1.1	142	170	5.6
110	60	F	25.1	170	100	N	N	N	Y	Y	35	1.0	118	180	6.5

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1.	42	M	22.1	130	80	Y	N				32	0.9	89	155	4.4
2.	43	M	22.3	120	70	N	N				33	0.9	77	134	4.9
3.	52	F	23.2	118	70	N	N				37	1.1	92	112	4.9
4.	41	F	22.1	116	70	N	N				26	1,3	98	125	3.2
5.	40	M	21.2	126	80	N	N				31	1,0	87	150	3.1
6.	39	M	22.4	110	76	N	N				36	1.2	66	126	3.6
7.	35	M	22.3	130	70	N	Y				37	1.0	75	146	4.6
8.	36	F	23.1	106	70	N	N				38	0.8	77	147	3.2
9.	42	F	23.4	110	80	N	Y				38	0.9	74	166	4.1
10.	50	M	23.5	112	80	N	N				39	0.7	73	155	5.0
11	51	M	22.5	126	80	N	Y				38	1.0	95	125	3.4
12	52	M	21.2	120	60	Y	N				37	0.8	78	123	3.8
13	54	F	21.8	130	70	N	N				32	0.8	98	142	3.5
14	47	F	22.8	120	80	N	N				30	0.9	123	152	4.5
15	45	M	23.1	118	76	N	N				28	0.9	87	148	3.4
16	44	M	22.0	116	80	Y	Y				31	1.0	92	156	3.5
17.	44	M	22.2	130	80	Y	Y				36	1.0	90	122	3.5
18.	43	F	20.3	120	80	N	N				37	0.9	91	144	3.6
19.	42	M	24.2	110	70	Y	N				32	0.8	114	142	4.5
20.	46	F	25.5	124	80	N	N				42	0.9	89	163	4.2

21	32	F	21.1	110	60	N	Y				34	1.0	106	152	3.8
22	37	M	23.2	130	70	N	Y				35	0.8	83	143	4.6
23	35	F	24.4	110	60	N	N				32	0.8	82	136	3.2
24	38	F	26.6	130	70	N	N				35	0.9	95	123	4.1
25	39	M	23.2	110	70	Y	N				32	0.7	130	142	3.3
26	43	M	23.2	122	80	Y	N				35	1.0	110	152	4.3
27	46	M	22.4	110	80	Y	N				34	0.8	124	143	3.6
28	47	F	23.1	106	70	N	N				32	0.8	112	120	4.5
29	37	M	25.5	120	60	N	N				31	0.9	118	122	3.7
30	33	M	22.5	120	80	Y	N				29	0.9	124	126	4.8
31	42	M	23.4	130	70	N	N				34	1.0	136	127	3.9
32	44	M	25.4	120	80	Y	N				35	1.0	123	128	4.4
33	48	F	24.5	110	90	N	Y				32	0.9	134	130	4.2
34	52	F	23.2	120	90	N	Y				38	0.9	122	124	3.1
35	63	M	25.5	120	80	Y	N				39	1.1	124	127	4.2
36	45	M	21.1	124	90	N	Y				32	1.2	89	149	4.1
37	60	M	23.2	110	70	N	N				30	1.0	126	132	3.4
38	65	F	24.4	130	80	N	N				72	2.8	84	120	4.7
39	44	M	22.6	120	70	N	N				27	0.9	91	134	3.6
40	61	F	23.2	110	60	N	Y				33	1.2	95	111	3.3
41	63	M	21.2	190	70	N	N				31	1.0	110	126	4.2
42	50	F	22.4	122	70	N	N				32	1.3	120	122	5.0

43	55	M	22.2	130	80	Y	N				30	1.0	134	124	4.4
44	46	M	22.2	120	80	Y	Y				32	1.0	132	132	3.1
45	42	F	22.4	116	80	N	N				41	1.0	118	143	4.3
46	43	M	23.1	110	70	N	N				33	0.8	114	125	4.6
47	36	M	25.5	120	80	Y	Y				29	1.0	126	120	5.5
48	34	M	22.5	110	60	N	N				28	0.8	113	146	4.3
49	38	F	21.4	120	70	N	N				29	0.9	124	123	4.7
50	42	M	22.4	140	80	Y	N				24	0.5	110	126	3.4
51	43	F	21.5	120	80	N	N				29	0.7	91	122	5.0
52	48	F	21.2	130	90	N	Y				32	0.8	82	143	5.1
53	35	F	22.6	110	90	N	N				33	1.2	83	160	4.2
54	39	M	21.5	110	90	Y	N				19	1.0	84	130	4.0
55	33	F	24.4	120	90	N	N				24	1.1	85	139	5.1